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| NEWS 25 | Sep 16 | Indexing added to some pre-1967 records in CA/CAPLUS |
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 14 Nov 2002 (20021114/PD)
FILE LAST UPDATED: 14 Nov 2002 (20021114/ED)
HIGHEST GRANTED PATENT NUMBER: US6481013
HIGHEST APPLICATION PUBLICATION NUMBER: US2002170103
CA INDEXING IS CURRENT THROUGH 14 Nov 2002 (20021114/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 14 Nov 2002 (20021114/PD)
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=> s toemifene
L1 0 TOEMIFENE

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L2 228 TOREMIFENE

=> s l2 and cardi?
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L3          113 L2 AND CARDI?

=> s l3 and cholestero?
          23858 CHOLESTERO?
L4           79 L3 AND CHOLESTERO?

=> s l4 and lumen
          30281 LUMEN
L5           15 L4 AND LUMEN

=> d l5 1-15 bib, ab, kwic

L5   ANSWER 1 OF 15  USPATFULL
AN      2002:236027  USPATFULL
TI      Methods and products related to pulmonary delivery of polysaccharides
IN      Liu, Dongfang, Framingham, MA, UNITED STATES
        Qi, Yiwei, Framingham, MA, UNITED STATES
        Venkataraman, Ganesh, Woburn, MA, UNITED STATES
        Sundaram, Mallikarjun, Brighton, MA, UNITED STATES
        Sasisekharan, Ram, Cambridge, MA, UNITED STATES
PA      Massachusetts Institute of Technology, Cambridge, MA, UNITED STATES
        (U.S. corporation)
PI      US 2002128225      A1   20020912
AI      US 2001-982548     A1   20011018 (9)
PRAI    US 2000-241559P     20001018 (60)
DT      Utility
FS      APPLICATION
LREP    Helen C. Lockhart, Wolf, Greenfield & Sacks, P.C., Federal Reserve
        Plaza, 600 Atlantic Avenue, Boston, MA, 02210
CLMN    Number of Claims: 112
ECL     Exemplary Claim: 1
DRWN    7 Drawing Page(s)
LN.CNT 2380
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      The invention relates to methods for delivering polysaccharides by a
        pulmonary route to achieve local and systemic therapeutic effects. The
        polysaccharides may be formulated or unformulated and in some instances
        have an extremely fast absorption rate.
SUMM    . . . glycosaminoglycans, and in particular heparin-like-
        glycosaminoglycans. Glycosaminoglycans have been established to be
        useful for treating and preventing coagulation disorders, thrombotic
        disorders, cardiovascular disease, vascular conditions,
        atherosclerosis, respiratory disorders, cancer, and angiogenic
        disorders.
SUMM    . . . and the therapeutic effect of the glycosaminoglycan is
        anti-coagulation or antithrombosis. In other embodiments the
        glycosaminoglycan is useful for treating cardiovascular
        disease, such as for instance, acute myocardial infarction, unstable
        angina, ischemic stroke, and atrial fibrillation, and vascular
        conditions, such as. . . surgical procedure or the subject is
        undergoing a tissue or organ transplant. Surgical procedures include but
        are not limited to cardiac-pulmonary by-pass surgery, coronary
        revascularization surgery, orthopedic surgery, and prosthesis
        replacement surgery.
DETD    . . . lung has the richest capillary network found in an organ in the
        human body, and the respiratory membrane separate capillary
        lumen from alveolar air space is very thin (.ltoreq.6 .mu.m) and
        extremely permissible. In addition, the liquid layer lining the
        alveolar. . .
DETD    . . . are useful. For instance, it is known that HLGAG compositions
```

are useful for preventing and treating coagulation, angiogenesis, thrombotic disorders, **cardiovascular** disease, vascular conditions, atherosclerosis, respiratory disorders, circulatory shock and related disorders, Alzheimer's disease, as well as inhibiting cancer cell growth. . .

DETD . . . to the tissue such as is seen for myocardial or cerebral infarction. Coagulation disorders include, but are not limited to, **cardiovascular** disease and vascular conditions such as cerebral ischemia.

DETD [0080] The methods of the invention are useful for treating **cardiovascular** disease. **Cardiovascular** diseases include, but are not limited to, acute myocardial infarction, unstable angina, and atrial fibrillation. Myocardial infarction is a disease. . .

DETD . . . emotional stress or following surgery, exercise, or acute alcoholic intoxication. Persistent forms of atrial fibrillation generally occur in patients with **cardiovascular** disease. Atrial fibrillation is characterized by disorganized atrial activity without discrete P waves on the surface ECG.

DETD [0082] The compounds of the invention can be used for the treatment of **cardiovascular** disorders alone or in combination with other therapeutic agents for reducing the risk of a **cardiovascular** disease or for treating the **cardiovascular** disease. Other therapeutic agents include, but are not limited to, anti-inflammatory agents, anti-thrombotic agents, anti-platelet agents, fibrinolytic agents, lipid reducing. . .

DETD . . . venous thromboembolism and pulmonary emboli and are well known in the art (e.g. see Hennekens et al, J Am Coll **Cardiol**; v. 25 (7 supp), p. 18S-22S (1995); Holmes, et al, J Am Coll **Cardiol**; v.25 (7 suppl), p. 10S-17S(1995)). Thrombolytic agents include, but are not limited to, plasminogen, a.sub.2-antiplasmin, streptokinase, antistreplase, tissue plasminogen activator. . .

DETD [0096] Pulmonary embolism as used herein refers to a disorder associated with the entrapment of a blood clot in the **lumen** of a pulmonary artery, causing severe respiratory dysfunction. Pulmonary emboli often originate in the veins of the lower extremities where. . .

DETD . . . for preventing the development of thrombosis associated with surgical procedures is contemplated. In addition to general surgical procedures such as **cardiac**-pulmonary by-pass surgery, coronary revascularization surgery, orthopedic surgery, prosthesis replacement surgery, and abdominal surgery, the methods are also useful in subjects. . .

DETD . . . based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as **cholesterol**, **cholesterol** esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel release systems; silastic systems; peptide based. . .

DETD . . . Streptonigrin; Streptozocin; Sulofenur; Talisomycin; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; **Toremifene** Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate;. . .

DETD . . . sodium citrate (1/9, v/v). Initially, 0.2 ml of citrated blood was added to Hemochron ACT test tubes containing glass particles ( **CardioMedical** Products, Rockaway, N.J.). Next, 0.2 ml of 0.025 M

CaCl.sub.2 was added to the test tube and the Hemochron-801 clot-timer machine (**CardioMedical** products, Rockaway, N.J.) was immediately started. The test tube was gently mixed for 10 sec., and inserted into the test. . .

CLM What is claimed:

. . . 18. The method of claim 17, wherein the coagulation disorder is selected from the group consisting of thrombosis associated with **cardiovascular** disease and vascular conditions.

19. The method of claim 18, wherein the **cardiovascular** disease is selected from the group consisting of acute myocardial infarction, unstable angina, and atrial fibrillation.

23. The method of claim 22, wherein the surgical procedure is selected from the group consisting of **cardiac**-pulmonary by-pass surgery, coronary revascularization surgery, orthopedic surgery, and prosthesis replacement surgery.

L5 ANSWER 2 OF 15 USPATFULL
AN 2002:152677 USPATFULL
TI Compounds and therapies for the prevention of vascular and non-vascular pathologies
IN Grainger, David J., Cambridge, UNITED KINGDOM
Metcalfe, James C., Cambridge, UNITED KINGDOM
Kasina, Sudhakar, Mercer Island, WA, United States
PA NeoRx Corporation, Seattle, WA, United States (U.S. corporation)
PI US 6410587 B1 20020625
AI US 2000-567558 20000505 (9)
RLI Continuation of Ser. No. US 1998-57323, filed on 9 Apr 1998, now patented, Pat. No. US 6117911
PRAI US 1997-43852P 19970411 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Lambkin, Deborah C.
LREP Schwegman, Lundberg, Woessner & Kluth, P.A.
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN 22 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 4577
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a method of treating a mammal having, or at risk of, an indication associated with a TGF-beta deficiency comprising administering one or more agents that is effective to elevate the level of TGF-beta. The invention also provides novel compounds that elevate TGF-beta levels, as well as pharmaceutical compositions comprising compounds that elevate TGF-beta levels, and methods for detecting diseases associated with endothelial cell activation.
SUMM . . . (Grainger et al., Biochem. J., 294, 109 (1993)) and aspirin (Grainger et al., Nat. Med., 1, 74 (1995)), can exhibit **cardioprotective** effects. However, the positive **cardioprotective** effects of these agents may be counterindicated by their potential side effects. TMX can cause liver carcinogenicity in rats, has. . .
SUMM . . . lupus erytematosus, and other auto-immune disorders. Such agents may also be useful to promote wound healing and to lower serum **cholesterol** levels.
SUMM . . . of an aspirinate that elevates the level of TGF-beta in said mammal so as to inhibit or reduce-diminution in vessel **lumen** diameter. Preferably, the levels of active TGF-beta are elevated after

administration of the aspirinate.

SUMM . . . of TGF-beta, preferably the level of active TGF-beta, in said mammal. Preferably, the administration inhibits or reduces diminution in vessel **lumen** diameter. The inhibition or reduction in diminution in vessel **lumen** diameter preferentially occurs at a site in a vessel where the vascular indication is, or is likely to be, manifested.. . . to bind to, or is capable of binding to, the TGF-beta receptor. This combination therapy can yield a significantly greater **cardiovascular** efficacy than would be expected from the administration of either agent singly. The therapeutic agents can act in a synergistic,. . .

SUMM . . . receptors. Thus, the agents of the invention are administered in a combined amount that prevents or inhibits diminution in vessel **lumen** diameter at, or near, a site or potential site of atherosclerotic lesion formation or development. A preferred first therapeutic agent. . .

SUMM The invention also provides a method to inhibit diminution in mammalian vessel **lumen** diameter. The method comprises administering to a mammal in need of said therapy, an amount of a first therapeutic agent. . . a second therapeutic agent effective to maintain or elevate the level of TGF-beta, so as to inhibit or reduce vessel **lumen** diminution. The inhibition or reduction in diminution in vessel **lumen** diameter preferentially occurs at a site in a vessel where the diminution is or is likely to be manifested. The. . .

SUMM . . . to the TGF-beta receptors. Agents useful to increase the level of latent TGF-beta include, but are not limited to, idoxifene, **toremifene**, raloxifene, droloxifene, ethynyl estradiol, diethylstibestrol, 1,25 dihydroxy-vitamin D3, retinoic acid and ligand pharmaceutical analogs thereof (Mukherjee et al. Nature, 1997,. . .

SUMM . . . enclosing, separately packaged, at least one device adapted for the delivery of a therapeutic agent to a site in the **lumen** of a mammalian vessel and at least one unit dosage form of a first therapeutic agent and one unit dosage. . .

DRWD FIG. 3 depicts the association of TGF-beta with different lipoprotein classes. Profile of lipoprotein particle elution measured as total **cholesterol** ( . . . ) and TGF-beta elution (open circles) following separation of the lipoprotein fraction (d<1.215 g/cm.sup.3) by gel. . .

DRWD FIG. 8 depicts the effect of tamoxifen (TMX) on various **cardiovascular** risk factors. A) Lipoprotein(a) amounts. B) Proportion of TGF-beta associated with the lipoprotein fraction.

DETD . . . pharmaceutically acceptable salt thereof, or a combination thereof, in an amount effective to inhibit or reduce the diminution in vessel **lumen** diameter in a diseased, e.g., atherosclerotic, or traumatized, e.g., due to stent placement, vessel.

DETD For the prevention of vessel **lumen** diminution associated with procedural vascular trauma, the therapeutic agent can be administered before, during or after the procedure, or any. . .

DETD . . . fatty acid, wherein said amount is effective to increase the level of TGF-beta so as to inhibit or reduce vessel **lumen** diameter diminution. The invention also provides for the administration of at least two therapeutic agents which together are effective to elevate the levels of TGF-beta in a mammal so as to inhibit or reduce vessel **lumen** diameter diminution. The invention also provides combination therapies to maintain elevated levels of TGF-beta in a mammal which is not. . .

DETD . . . amount effective to increase TGF-beta levels. The increase in TGF-beta levels, in turn, inhibits or reduces the diminution in vessel **lumen** diameter in a diseased, e.g., atherosclerotic, or traumatized, e.g., due to stent placement, vessel. The increase in

TGF-beta levels can. . .

DETD . . . kit comprising a catheter adapted for the local delivery of at least one therapeutic agent to a site in the **lumen** of a mammalian vessel, along with instruction means directing its use in accord with the present invention. Preferably, the therapeutic. . .

DETD . . . second agents may be introduced via discrete lumens of a catheter, or mixed together prior to introduction into a single **lumen** of a catheter. If the unit dosage forms are introduced into discrete lumens of a catheter, the delivery of the agents to the vessel can occur simultaneously or sequentially. Moreover, a single **lumen** catheter may be employed to deliver a unit dosage form of one agent, followed by the reloading of the **lumen** with another agent and delivery of the other agent to the **lumen** of the vessel. Either or both unit dosages can act to reduce the diminution in vessel **lumen** diameter at the target site.

DETD "**Cholesterol** lowering agents" include agents which are useful for lowering serum **cholesterol** such as for example bile acid sequestering resins (e.g. colestipol hydrochloride or cholestyramine), fibric acid derivatives (e.g. clofibrate, fenofibrate, or. . .

DETD . . . as well as other auto-immune disorders. Non-vascular indications also include the promotion of wound healing and the lowering of serum **cholesterol** levels.

DETD . . . carbon atom from the methyl end of the fatty acid chain. These fatty acids have been proposed to yield significant **cardiovascular** protection (Burr et al., Lancet, 221, 757 (1989)). Omega-3 fatty acids include 5,8, 11, 14, 17-eicosapentaenoic acid and docosahexaenoic acid.. . .

DETD "Vascular indication" includes, but is not limited to, a **cardiovascular** disease, e.g., atherosclerosis, thrombosis, myocardial infarction, and stroke, or a **cardiovascular** condition, e.g., vessels subjected to trauma associated with interventional procedures ("procedural vascular trauma"), such as restenosis following angioplasty, placement of. . . term "vascular indication" is non-coronary vessel disease, such as arteriolosclerosis, small vessel disease, nephropathy, greater than normal levels of serum **cholesterol**, asthma, hypertension, emphysema and chronic obstructive pulmonary disease. "Vascular indication" does not include cancer, including smooth muscle cell carcinomas or. . .

DETD . . . of TGF-beta protein include, but are not limited to, moieties which affect the nuclear hormone receptor pathway (e.g., tamoxifen, idoxifene, **toremifene**, raloxifene, droloxifene and other anti-estrogen analogues of tamoxifen, ethynyl estradiol, diethylstilbestrol, other synthetic estrogen agonists and compounds disclosed in U.S.. . .

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats. These studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by the non-TMX analogs of formula (VI), including the TMX analog **toremifene**, and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD . . . TGF-beta activators or production stimulators or lead compounds, including other known stilbene-type antisteroids such as for example, cis- and trans-clomiphene, **toremifene**, centchroman, raloxifene, droloxifene, (1-[4-(2-dimethylaminoethoxy)phenyl]-1-(3-

hydroxyphenyl)-2-phenyl-2-butene (see U.S. Pat. No. 5,384,332), 1-nitro-1-phenyl-2-(4-hydroxyphenyl or anisyl)-2-[4-(2-pyrrol-N-ylethoxy)-phenyl]ethylene(CN-55,945),trans-1,2-dimethyl-1,2-(4-hydroxyphenyl)ethylene(trans-dimethylstilboestrol), trans-diethylstilboestrol, and 1-nitro-1-phenyl-2-(4-hydroxyphenyl)-2-[4-(3-dimethylaminopropyloxy)phenyl-ethylene (GI680), metabolites or pharmaceutically acceptable. . .

DETD . . . expressing the human apo(a) transgene that are fed a high fat diet, apoE knockout mice fed a normal diet, or **cholesterol**-fed Watanabe rabbits.

DETD . . . a backing layer and a polymer matrix which has dispersed or dissolved therein a therapeutic agent effective for reducing vessel **lumen** diameter diminution, along with one or more skin permeation enhancers. The backing layer can be made of any suitable material. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . by polymeric endoluminal sealing. This technique uses a catheter to apply a polymeric implant to the interior surface of the **lumen**. The therapeutic agent incorporated into the biodegradable polymer implant is thereby released at the surgical site. This technique is described. . .

DETD . . . of an aspirinate effective to elevate the level of TGF-beta so as to inhibit or reduce the diminution of vessel **lumen** diameter. Specifically, the administration is effective to reduce or prevent lipid accumulation by the vessel, to increase plaque stability of. . .

DETD A further aspect of the invention provides a therapeutic method for lowering serum **cholesterol**, comprising administering to a mammal in need of such therapy, an effective amount of an aspirinate.

DETD . . . a kit comprising, separately packaged, a device adapted for the local delivery of an agent to a site in the **lumen** of a vessel of a mammal, and at least one unit dosage form of an aspirinate, wherein the aspirinate is. . .

DETD . . . wherein said amount is effective to maintain or increase the level of TGF-beta so as to inhibit or reduce vessel **lumen** diameter diminution.

DETD . . . comprising, separately packaged, a device adapted for the local delivery of at least one agent to a site in the **lumen** of a mammalian vessel and at least one unit dosage of aspirin or an aspirinate and at least one unit. . .

DETD The total **cholesterol** in each fraction was measured by the **cholesterol** oxidase enzymatic method (Sigma Diagnostics) as previously described in Grainger et al., Nat. Med., 1, 1067 (1995). The **cholesterol** in fractions 0-9 was assumed to be VLDL, in fractions 10-19 to be LDL, and in factions 20-30 to be HDL, in accordance with the elution positions of the major apolipoproteins. Lipoprotein concentrations are reported as mM **cholesterol**. For cell cultures studies, the lipoprotein fraction was subjected to extensive dialysis against serum-free DMEM, and the amount of TGF-beta. . .

DETD . . . ka for TGF-beta binding to R2X to a maximal value of 42.+-.6 ng/ml when lipoprotein equivalent to 3 mM total **cholesterol** was added (FIG. 2A; values are the mean.+-.standard error of triplicate determinations). The concentration of lipoprotein (measured as total **cholesterol**) which half-maximally increased the apparent ka was approximately 1 mM. Thus, TGF-beta which is associated with lipoprotein particles has a. . .

DETD . . . caused a dose-dependent increase in the ID.sub.50 of TGF-beta. The ID.sub.50 was maximal at 0.52.+-.0.08 ng/ml when 3 mM total **cholesterol** was added. The concentration of lipoprotein which half-maximally increased the ID.sub.50 was approximately 0.8 mM. Therefore, TGF-beta associated with lipoprotein. . .

DETD . . . the lipoprotein-associated TGF-beta eluted with a tightly defined subfraction of the HDL particles, with the smallest size of all the **cholesterol**-containing lipoprotein particles. The remaining 12% of the lipoprotein-associated TGF-beta was distributed among the VLDL and LDL fractions. This pattern of. . .

DETD Individual K was a diabetic patient with hypertriglyceridaemia, and >50% of the total plasma **cholesterol** was present in the largest triglyceride-rich lipoprotein particles (FIG. 3C). This individual had 78% of the plasma TGF-beta associated with. . .

DETD . . . TGF-beta associates with a subtraction of HDL particles which vary very little in size and which are among the smallest **cholesterol**-containing lipoproteins present in plasma. Additionally, TGF-beta can associate with both the triglyceride-rich LDL and VLDL particles (FIG. 10). Indeed, under. . .

DETD At the end of the four week supplementation period total plasma triglyceride concentrations were somewhat reduced although total plasma **cholesterol** was unaffected (FIG. 4; Table 2). Fish oil supplementation also markedly reduced TGF-beta association with the lipoprotein fraction. The mean. . .

DETD . . . TGF-beta but increases TGF-beta bioavailability by decreasing the lipoprotein sequestration of the TGF-beta. Such an effect would likely result in **cardioprotection** in individuals with adequate production of latent and mature TGF-beta but limited ability to release TGF-beta from lipoprotein complexes.

DETD
TABLE 2

| Time (weeks) | Fish oil supplementation | Total triglyceride (mM) | Total **cholesterol** (mM) | % associated TGF-beta |
|---|---|---|---|---|
| 0 | None | 1.43 .+-. 0.43 | 5.1 .+-. 1.2 | 19 .+-. 10 |
| | n = 32 | | | |
| 4 | 2.4 g/day. . . | | | |

DETD . . . following dietary supplementation with fish oil. Total triglyceride concentration was measured by the glycerol kinase enzymatic method (Sigma Diagnostics). Total **cholesterol** and % associated TGF-beta were assayed as described in Example I. Values are mean.+-.standard error. * p<0.01; paired Wilcoxon signed-rank. . .

DETD Aspirin has been suggested to have **cardioprotective** effects and is now in widespread use by patients diagnosed with coronary atherosclerosis. It has been demonstrated to significantly reduce. . .

DETD A number of effects have been suggested to play a role in the **cardioprotective** benefits associated with chronic use of low-dose aspirin. Aspirin interferes with normal platelet function and increases the blood clotting time,. . . formation is the main cause of MI, the anti-platelet function of aspirin is thought to be important in mediating its **cardioprotective** effects. Moreover, since aspirin is a well-documented anti-inflammatory agent and atherosclerosis has an important inflammatory component, the anti-inflammatory action of aspirin could also contribute to **cardioprotection**.

DETD Consumption of red wine has been proposed to mediate **cardiovascular** protection, although the data supporting this proposal are still debated. To determine whether red wine, as opposed to white wine,. . .

DETD Total plasma triglyceride, total plasma **cholesterol**, HDL-**cholesterol**, LDL-**cholesterol** and VLDL-**cholesterol** were routinely assayed in all patients. Liver function tests (aspartate transaminase and lactate dehydrogenase) were also performed on samples prior. . .

DETD
TABLE 3

| | Day 0 | Day 10 |
|---|---|---|
| Age (yrs) | 62.2 .+-. 1.5 | |
| Total plasma **cholesterol** (mM) | 6.31 .+-. 0.28 | 5.95 .+-. 0.29* |
| VLDL-**cholesterol** (mM) | 1.03 .+-. 0.14 | 0.84 .+-. 0.11* |
| LDL-**cholesterol** (mM) | 4.48 .+-. 0.27 | 4.16 .+-. 0.25 |
| HDL-**cholesterol** (mM) | 0.78 .+-. 0.03 | 0.77 .+-. 0.04 |
| Total plasma triglycerides (mM) | 2.79 .+-. 0.44 | 2.28 .+-. 0.35 |
| Plasma (a + 1) TGF-.beta. (ng/ml) | | |

Method (A). . .

DETD Another **cardiovascular** risk factor which has been shown to influence TGF-beta activity is the lipoprotein profile, since TGF-beta can be sequestered into lipoprotein particles where it is biologically inactive. TMX has been reported to decrease plasma **cholesterol** and to increase the fraction of **cholesterol** in HDL particles. Consistent with these reports, total plasma **cholesterol** was decreased by 6% below baseline (p=0.04) after 10 days of TMX therapy. In addition, **cholesterol** in the VLDL fraction was reduced (18% below baseline; p=0.04) but the concentration of LDL-**cholesterol** and HDL-**cholesterol** were both unchanged (Table 3). Total plasma triglyceride concentration was 18% lower after 10 days of TMX treatment, but the. . .

DETD Another disadvantage of aspirin as a **cardiovascular** agent, besides the fact that it is not a very potent TGF-beta elevating agent, is that it appears to be. . .

DETD . . . aspirin and fish oil, 8-week-old female apoE knockout mice were fed aspirin or fish oil, or both, to assess the **cardioprotective** effects of modulating different components of the TGF-beta pathway.

DETD . . . Dohme) at 400 .mu.g/kg/day (2 .mu.g/g food). Simvastatin is an inhibitor of the enzyme HMG-CoA reductase, the committed step in **cholesterol** biosynthesis. As a result, it has been shown to reduce the total plasma **cholesterol** concentration in man and in particular the concentration of **cholesterol** in the more triglyceride-rich particles (VLDL and LDL). If alterations in the lipid profile are responsible for the suppression of. . .

DETD . . . greater the inhibition of lesion development. This correlation provides powerful evidence supporting the role of TGF-beta activity in mediating the **cardioprotective** activity of both tamoxifen, and aspirin and fish oil.

DETD The effect of each treatment on the lipid profile of each group of mice was determined by measuring the **cholesterol** and triglyceride. Blood from a terminal bleed was collected in a polypropylene tube, allowed to clot at room temperature for. . . hours and then spun (1,000.times.g; 5 minutes). The serum supernatant was aliquoted and stored at -20.degree. C. until assayed. Total **cholesterol** and total triglycerides were determined for each mouse using the **cholesterol** oxidase and glycerol kinase UV end-point enzymatic methods respectively (Sigma Diagnostics). For determination of the

lipoprotein profile, 100 .mu.l of. . . filtration FPLC chromatography on a Sepharose 6B column, and the elution positions of the lipoprotein particles were detected by measuring **cholesterol** (by the **cholesterol** oxidase enzymatic method) in each fraction. VLDL particles eluted in fractions 1-10, LDL in fractions 11-20 and HDL in fractions. . .

DETD Treatment of the mice with aspirin for three months had no effect on total plasma **cholesterol** or on the lipoprotein profile (Table 8). Mice treated with diets containing fish oil (with or without aspirin) had similar total plasma **cholesterol** and triglyceride concentrations to control mice, although there was a small reduction in the concentration of both VLDL-**cholesterol** (-16%/) and LDL-**cholesterol** (-12%/) and an increase in HDL-**cholesterol** (+10%/). Consistent with the effects of dietary supplementation with fish oil in man, a decrease in **cholesterol**, primarily in the VLDL fraction, in apoE knockout mice treated with fish oil was observed.

DETD There was a significant reduction in total plasma **cholesterol** in apoE knockout mice treated with simvastatin (-27%; $p<0.01$; n=10; Students unpaired t-test). Much of this reduction occurred in the VLDL fraction (-14%) and LDL fraction (-41%), with an increase in HDL-**cholesterol**. In contrast, TMX lowered VLDL by seven fold and is a much more powerful lipid-lowering agent in the apo(E)-/- mouse. . .

DETD

TABLE 9

| | Group A | Group B | Group C | Group D | Group E | Group F |
|---|---|---|---|---|---|---|
| Total **cholesterol** (mg/dl) | n.d. | 306 .+-. 31 | 282 .+-. 28 | 273 .+-. 19 | 266 .+-. 25 | 224 .+-. 29** |
| Total triglyceride (mg/dl) | n.d. | 302 .+-. 28 | 320 .+-. 19 | 308 .+-. 25 | 296 .+-. 33 | 266 .+-. 14** |
| VLDL-**cholesterol** (mg/dl) | n.d. | 184 | 179 | 157 | 151 | 158 |
| LDL-**cholesterol** (mg/dl) | n.d. | 92 | 89 | 91 | 88 | 54 |
| HDL-**cholesterol** (mg/dl) | n.d. | 30 | 26 | 32 | 33 | 35 |

**p < 0.001; Mann-Whitney U test
n.d. = not determined.
A single measurement of. . .

DETD . . . formation. If low dose aspirin therapy and dietary supplementation with fish oil differ in their mechanism of action, then their **cardioprotective** effects would be expected to be additive. However, the results described hereinabove provide evidence that the combination of aspirin and. . . a markedly synergistic effect. Thus, a combination of low dose aspirin and fish oil therapy can be very useful in **cardiovascular** disease prevention. Moreover, because fish oil is not a very effective VLDL lowering agent, more powerful VLDL lowering agents, such as TMX, can be employed in combination therapies with aspirin, aspirinate salts to result in more beneficial **cardiovascular** effects.

DETD . . . transgenic mouse models of atherosclerosis (Grainger et al.). However, tamoxifen has a variety of other effects, including reducing total plasma **cholesterol** and inducing some weight loss, which may have contributed to the observed reduction in lesion development. As a result, it. . .

DETD . . . tissue and the subsequent damage or destruction of that tissue by chronic inflammation. Preferred ER/NFkB modulators include idoxifene, raloxifene, droloxifene, **toremifene**, and tamoxifen, as well as functional equivalents, analogs or derivatives thereof. These agents also inhibit or reduce TNF-alpha mediated NFkB. . .

DETD Effects of the Therapeutic Agents on **Cholesterol** Levels
DETD Twenty six patients with high **cholesterol** were administered simnvastatin for 16 weeks. Blood was collected at six times points during the 16 weeks and analyzed for TGF-beta levels. While serum **cholesterol** levels were reduced in these patients, there was no effect on TGF-beta levels in any of the patients. In contrast,. . . the patients participating in a trial in which tamoxifen, a tamoxifen analog, or placebo, was administered, showed significant decreases in **cholesterol** levels. Therefore, a combination of one of the therapeutic agents of the invention and an agent which lowers serum **cholesterol** levels may exert a synergistic effect and thus, may be useful in the practice in the methods of the invention. Moreover, therapeutic agents of the invention alone may be useful to lower serum **cholesterol** levels.
CLM What is claimed is:
8. A therapeutic method for lowering serum **cholesterol** comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula VI: ##STR24##. . .
26. A therapeutic method for lowering serum **cholesterol** comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula VI: ##STR34##. . .

L5 ANSWER 3 OF 15 USPATFULL
AN 2002:133873 USPATFULL
TI Prevention and treatment of **cardiovascular** pathologies with tamoxifen analogues
IN Grainger, David J., Cambridge, UNITED KINGDOM
Metcalfe, James C., Cambridge, UNITED KINGDOM
Kunz, Lawrence L., Redmond, WA, UNITED STATES
Schroff, Robert W., Edmonds, WA, UNITED STATES
PA NeoRx Corporation (non-U.S. corporation)
PI US 2002068731 A1 20020606
AI US 2001-754775 A1 20010104 (9)
RLI Continuation of Ser. No. US 1997-973570, filed on 5 Dec 1997, GRANTED, Pat. No. US 6197789 A 371 of International Ser. No. WO 1996-US10211, filed on 7 Jun 1996, UNKNOWN Continuation-in-part of Ser. No. US 1995-478936, filed on 7 Jun 1995, ABANDONED Continuation-in-part of Ser. No. US 1995-476735, filed on 7 Jun 1995, GRANTED, Pat. No. US 5595722 Continuation-in-part of Ser. No. US 1995-477393, filed on 7 Jun 1995, PENDING Continuation-in-part of Ser. No. US 1995-486334, filed on 7 Jun 1995, GRANTED, Pat. No. US 5770609
DT Utility
FS APPLICATION
LREP SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A., P.O. BOX 2938, MINNEAPOLIS, MN, 55402
CLMN Number of Claims: 121
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 4207
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##

wherein Z is C.dbd.O or a covalent bond; Y is H or O(C.sub.1-C.sub.4)alkyl, R.sup.1 and R.sup.2 are individually (C.sub.1-C.sub.4)allyl or together with N are a saturated heterocyclic group, R.sup.3 is ethyl or chloroethyl, R.sup.4 is H, R.sup.5 is I, O(C.sub.1-C.sub.4)alkyl or H and R.sup.6 is I, O(C.sub.1-C.sub.4)alkyl or H with the proviso that when R.sup.4, R.sup.5, and R.sup.6 are H, R.sup.3 is not ethyl; or a pharmaceutically acceptable salt thereof,

effective to elevate the level of TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compounds include idoxifene, **toremifene** or salts thereof. Further provided is a method for identifying an agent that elevates the level of TGF-beta. Another embodiment of the invention is an assay or kit to determine TGF-beta in vitro. Also provided is a therapeutic method comprising inhibiting smooth muscle cell proliferation associated with procedural vascular trauma employing the administration of tamoxifen or structural analogs thereof, including compounds of formula (I).

TI Prevention and treatment of **cardiovascular** pathologies with tamoxifen analogues

AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##

AB . . . TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compounds include idoxifene, **toremifene** or salts thereof. Further provided is a method for identifying an agent that elevates the level of TGF-beta. Another embodiment. . .

SUMM [0001] This invention relates generally to the prevention and treatment of **cardiovascular** pathologies. More specifically, a method for treating or preventing atherosclerosis is provided.

SUMM . . . in many patients with coronary artery disease. PTCA can relieve myocardial ischemia in patients with coronary artery disease by reducing **lumen** obstruction and improving coronary flow. The use of this surgical procedure has grown rapidly, with 39,000 procedures performed in 1983,. . .

SUMM [0006] In general, atherosclerosis is a **cardiovascular** disease in which the vessel wall is remodeled, compromising the **lumen** of the vessel. The atherosclerotic remodeling process involves accumulation of cells, both smooth muscle cells and monocyte/macrophage inflammatory cells, in. . .

SUMM [0008] Thus, a need exists for therapeutic methods and agents to treat **cardiovascular** pathologies, such as atherosclerosis and other conditions related to coronary artery disease.

SUMM [0009] A therapeutic method for preventing or treating a **cardiovascular** or vascular indication characterized by a decreased **lumen** diameter is provided. The method comprises administering to a mammal at risk of, or afflicted with, said **cardiovascular** indication, a cytostatic dose of a therapeutic agent that elevates the level of TGF-beta, such as a compound of formula. . .

SUMM [0011] A therapeutic method is provided for treating or preventing **cardiovascular** pathologies, such as conditions selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke. The method comprises the. . .

SUMM [0014] A further embodiment of the invention is a method for preventing **cardiovascular** pathologies in a mammal at risk of such a condition. Such conditions include atherosclerosis, thrombosis, myocardial infarction, and stroke. The. . .

SUMM [0019] The delivery of an agent that elevates the level of TGF-beta, e.g., TGF-beta activators or production stimulators, to the **lumen** of a vessel via catheter, before, during or after angioplasty, is discussed in detail below. A stent or shunt useful. . .

SUMM [0030] In addition, methods for using TGF-beta to maintain and increase vessel **lumen** diameter in a diseased or injured mammalian vessel are described.

SUMM . . . the proliferation of vascular tissue. A preferred embodiment of the invention includes the administration of idoxifene, 3-iodotamoxifen,

4-iodotamoxifen, raloxifene, droloxifene, **toremifene**, or a pharmaceutically acceptable salt thereof.

DRWD [0036] FIG. 4 depicts the association of TGF-beta with different lipoprotein classes. Profile of lipoprotein particle elution measured as total **cholesterol** ( . . . ) and TGF-beta elution (open circles) following separation of the lipoprotein fraction (d<1.215 g/cm.sup.3) by gel. . .

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats and these studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by the non-TMX analogs of formula (I), including the TMX analog **toremifene** and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD [0047] Also included within the scope of the term tamoxifen are the TMX structural analogs **toremifene** and raloxifene, metabolites or pharmaceutically acceptable salts thereof. Other "antisteroids" or "steroidal antagonists" can also be useful as agents that. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . suppressing the pathological proliferation of the target cell population. The preferred dosage forms can also release compounds that increase vessel **lumen** area and blood flow, reducing the pathological alterations produced by this reduced blood supply.

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the tunica media smooth muscle cells lining the **lumen** to the dosage form. This dosage is determinable empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD [0140] In hypertension, there is increased thickness of the vessel media, with a consequent decrease in maximum **lumen** diameter, leading to increased vascular resistance. The increased thickness of the vessel media is due to growth of VSMC within. . .

DETD . . . proliferate in the intima. There they secrete extracellular matrix proteins and form a lipid-rich plaque that encroaches on the vascular **lumen**. This process is similar to, but slower than, the process that occurs following PTCA, leading to restenosis. Such inappropriate intimal. . .

DETD . . . diet, and also in apoE knockout mice fed a normal diet. Another animal model useful in screening agents is the **cholesterol**-fed Watanabe rabbit. Finally, small scale, pilot studies on candidate molecules are tested in patient groups with clinically significant coronary artery. . .

DETD . . . In addition, heparin coupled to agarose beads (Sigma Chemical Co., St. Louis, Mo.) was examined (see also Grainger et al., **Cardiovascular** Res. 27: 2238-47, 1993).

DETD . . . whether the mice were fed a normal diet (Techlad, Madison, Wis.; 4% mouse/rat chow) or a lipid-rich diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium chelate.

DETD . . . by increasing TGF-.beta. activity, such as TMX (Grainger et al., Biochem. J., 224, 109 (1993)) and heparin (Grainger et al., **Cardiovas**. Res., 27, 2238 (1993)), inhibited the proliferation of EX but not ED cells.

DETD . . . in groups were weighed then fed ad libitum either normal mouse chow (ICN/Flow), or a high fat diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium cholate, or high fat diet containing 15 .mu.g TMX. . .

DETD . . . The column was eluted with buffer A at 0.4 ml/minute and fractions of 0.2 ml were collected and analyzed for **cholesterol**. **Cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) by adding 5 .mu.l from each column fraction to 200 .mu.l assay reagent in an ELISA. . . incubated at 37.degree. C. for 15 minutes and absorbance read at 492 nm. Serum for calibration containing 200 mg/dL total **cholesterol** (Sigma Diagnostics) was used to convert absorbance readings to **cholesterol** concentrations according to the manufacturer's instructions. The positions of elution of the major lipoprotein classes in mouse platelet-poor plasma under. . .

DETD [0275] Assays for Plasma Triglycerides, **Cholesterol** and Sex Hormones

DETD [0276] Total plasma triglycerides was measured by the UV end-point glycerol kinase enzyzatic method (Sigma Diagnostics). Total plasma **cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) performed in ELISA plate wells as described above. 17-.beta.-estradiol was measured by a specific sandwich ELISA. .

DETD . . . on either a normal mouse chow (low fat diet), or a high fat chow containing 0.5% sodium cholate and 5% **cholesterol** (high fat diet), or high fat diet containing 15 .mu.g/g TMX (high TMX diet). The mice on the high TMX. . .

DETD . . . 3 13 .+-. 5 11 .+-. 7

| | | | | |
|---|---|---|---|---|
| Testosterone (ng/ml) | | | | |
| Total Plasma | 71 .+-. 2 | 92 .+-. 4 | 79 .+-. 3** | 83 .+-. 4*** |
| **Cholesterol** (mg/dl) | | | | |
| VLDL | 4 | 30 | 38 | 42 |
| **Cholesterol** (mg/dl) | | | | |
| LDL | 8 | 33 | 27 | 27 |
| **cholesterol** (mg/dl) | | | | |
| HDL- | 58 | 27 | 11 | 14 |
| **cholesterol** (mg/dl) | | | | |
| Total | 142 .+-. 15 | 109 .+-. 5* | 111 .+-. 9 | 204 .+-. 36*** |
| Triglycerides (mg/dl) | | | | |
| SM-.alpha.-actin | 146 .+-. 6 | 138 .+-. 8 | 168 .+-.. . . | |

DETD [0283] High or low TMX diets significantly lowered total plasma **cholesterol** by approximately 10% compared with mice on the high fat diet. Analysis of the lipoprotein profiles showed that for the mice on the low fat diet, most of the **cholesterol** was in the HDL fraction. After 3 months on the high fat diet, however, there was a marked increase in very low density lipoprotein (VLDL) **cholesterol** of approximately 7-fold (Table 2) and LDL **cholesterol** (4-fold) whereas the amount of **cholesterol** in the HDL fraction was reduced by approximately 50% (Table 2). The high and low TMX diets had only small effects on the amount of **cholesterol** in VLDL or LDL, but further reduced the HDL **cholesterol** by approximately 50% (Table 2), accounting for most

of the overall reduction in **cholesterol**. In contrast to the decrease in total plasma **cholesterol** concentration caused by the high TMX diet, there was an increase in plasma concentration of triglyceride (Table 2).

DETD . . . subsequently uptake of lipid by the activated cells when the mice are subjected to a high fat diet. Thus, the **cardiovascular** protective effect of TMX in mice may be due to elevation of TGF-.beta. in the artery wall which prevents VSMC. . . TMX would prevent lipid lesion formation in apo(a) mice on a high fat diet. It is of interest that the **cardiovascular** protective effects of TMX against diet-induced lipid lesions in mice reported here were obtained at doses similar to those used. . .

DETD . . . manufacturer's instructions. The proportion of TGF-beta in the lipoprotein fraction is shown in Table 8 (% associated TGF-beta). The total **cholesterol** in each fraction was measured by the **cholesterol** oxidase enzymatic method (Sigma Diagnostics) as previously described in Grainger et al., Nat. Med., 1, 1067 (1995). The **cholesterol** in fractions 0-9 was assumed to be VLDL, in fractions 10-19 to be LDL, and in fractions 20-30 to be HDL, in accordance with the elution positions of the major apolipoproteins. Lipoprotein concentrations are reported as mM **cholesterol**.

DETD . . . ka for TGF-beta binding to R2X to a maximal value of 42.+-.6 ng/ml when lipoprotein equivalent to 3 mM total **cholesterol** was added (FIG. 3A). Values are the mean .+-. standard error of triplicate determinations. The concentration of lipoprotein (measured as total **cholesterol**) which half-maximally increased the apparent ka was approximately 1 mM. Thus, the TGF-beta associated with the lipoprotein particles has a. . .

DETD . . . caused a dose-dependent increase in the ID.sub.50 of TGF-beta. The ID.sub.50 was maximal at 0.52.+-.0.08 ng/ml when 3 mM total **cholesterol** was added. The concentration of lipoprotein which half-maximally increased the ID.sub.50 was approximately 0.8 mM. Therefore, TGF-beta associated with lipoprotein. . .

DETD . . . the lipoprotein-associated TGF-beta eluted with a tightly defined subfraction of the HDL particles, with the smallest size of all the **cholesterol**-containing lipoprotein particles. The remaining 12% of the lipoprotein-associated TGF-beta was distributed among the VLDL and LDL fractions. This pattern of. . .

DETD [0348] Individual K was a diabetic patient with hypertriglyceridaemia, and >50% of the total plasma **cholesterol** was present in the largest triglyceride-rich lipoprotein particles (FIG. 4C). This individual had 78% of the plasma TGF-beta associated with. . .

DETD . . . TGF-beta associates with a subfraction of HDL particles which vary very little in size and which are among the smallest **cholesterol**-containing lipoproteins present in plasma. Additionally, TGF-beta can associate with both the triglyceride-rich LDL and VLDL particles, which can contain the. . .

CLM What is claimed is:

2. A method comprising administering to a mammal at risk of a **cardiovascular** condition the following: an effective amount of a compound of formula (I) ##STR4## wherein Z is C.dbd.O or a covalent. . . ethyl; or a pharmaceutically acceptable salt thereof, wherein the amount is administered over time to the mammal to prevent a **cardiovascular** condition selected from the group consisting of thrombosis, myocardial infarction, and stroke.

10. The method of claim 1 or 2 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a pharmaceutically acceptable salt thereof.

12. The method of claim 1 or 2 wherein the compound of formula (I) is **toremifene** or a pharmaceutically acceptable salt thereof.

. . . kit comprising, separately packaged, a catheter adapted for the local delivery of a therapeutic agent to a site in the **lumen** of a mammalian vessel and a unit dosage of a therapeutic agent of formula (I): ##STR6## wherein Z is C.dbd.O. . .
36. The kit of claim 32 wherein the therapeutic agent of formula (I) is **toremifene** or a pharmaceutically acceptable salt thereof.

. . . kit comprising, separately packaged, a catheter adapted for the local delivery of a therapeutic agent to a site in the **lumen** of a mammalian vessel and a unit dosage of droloxifene and pharmaceutically acceptable salts thereof, wherein the unit dosage is. . .
70. The method of claim 65 or 66 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a pharmaceutically acceptable salt thereof.

72. The method of claim 21, 65, 66 or 67 wherein the compound of formula (I) is **toremifene** or a pharmaceutically acceptable salt thereof.

84. A therapeutic method for preventing or treating a **cardiovascular** or vascular indication characterized by a decreased **lumen** diameter comprising administering to a mammal at risk of or afflicted with said **cardiovascular** indication, a cytostatic dose of a therapeutic agent, wherein the therapeutic agent is a compound of formula (I): ##STR10## wherein. . .
86. The method of claim 84 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a pharmaceutically acceptable salt thereof.

88. The method of claim 84 wherein the compound of formula (I) is **toremifene** or a pharmaceutically acceptable salt thereof.

95. The method of claim 94 wherein the structural analog of tamoxifen is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, raloxifene, droloxifene, **toremifene**, or a pharmaceutically acceptable salt thereof.

96. The method of claim 94 wherein the structural analog of tamoxifen is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a pharmaceutically acceptable salt thereof.

98. The method of claim 94 wherein the structural analog of tamoxifen is **toremifene**, or a pharmaceutically acceptable salt thereof.

109. The method of claim 93 wherein the compound is **toremifene** or a pharmaceutically acceptable salt thereof.

119. The method of claim 116 wherein the agent is **toremifene** or a pharmaceutically acceptable salt thereof.

L5 ANSWER 4 OF 15 USPATFULL
AN 2002:126317 USPATFULL
TI Human tumor necrosis factor delta and epsilon
IN Yu, Guo-Liang, Berkeley, CA, UNITED STATES
Ni, Jian, Germantown, MD, UNITED STATES
Gentz, Reiner L., Rockville, MD, UNITED STATES
Dillon, Patrick J., Carlsbad, CA, UNITED STATES

PA Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (U.S. corporation)
PI US 2002064829 A1 20020530
AI US 2001-879919 A1 20010614 (9)
RLI Continuation-in-part of Ser. No. US 1997-815783, filed on 12 Mar 1997, PENDING
PRAI US 1996-16812P 19960314 (60)
US 2001-293499P 20010525 (60)
US 2001-277978P 20010323 (60)
US 2001-276248P 20010316 (60)
US 2000-254875P 20001213 (60)
US 2000-241952P 20001023 (60)
US 2000-211537P 20000615 (60)
DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 62
ECL Exemplary Claim: 1
DRWN 11 Drawing Page(s)
LN.CNT 13531
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to human TNF delta and TNF epsilon polypeptides, polynucleotides encoding the polypeptides, methods for producing the polypeptides, in particular by expressing the polynucleotides, and agonists and antagonists of the polypeptides. The invention further relates to methods for utilizing such polynucleotides, polypeptides, agonists and antagonists for applications, which relate, in part, to research, diagnostic and clinical arts.

SUMM . . . shock, gastrointestinal cancers, pancreatitis, dermatitis, gout, systemic lupus erythematosis, and Grave's disease. Inflammation is also a potentially life-threatening complication of **cardiopulmonary** bypass surgery, renal ischemia-reperfusion, and traumatic injury.

SUMM . . . (e.g., HAV, HBV, HCV, etc.), Helicobacter pylori infection, invasive Staphylococcia, etc.), parasitic infection, nephritis, bone disease (e.g., osteoporosis), atherosclerosis, pain, **cardiovascular** disorders (e.g., neovascularization, hypovascularization or reduced circulation (e.g., ischemic disease (e.g., myocardial infarction, stroke, etc.))), AIDS, allergy, inflammation, neurodegenerative disease. . . multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, immune complex glomerulonephritis, autoimmune diabetes, autoimmune thrombocytopenic purpura, Grave's disease, Hashimoto's thyroiditis, etc.), **cardiomyopathy** (e.g., dilated **cardiomyopathy**), diabetes, diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy), influenza, asthma, psoriasis, glomerulonephritis, septic shock, and ulcerative colitis.

DETD [0202] For secretion of the translated protein into the **lumen** of the endoplasmic reticulum, into the periplasmic space or into the extracellular environment, appropriate secretion signals may be incorporated into. . .

DETD . . . on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4 hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, **toremifene** (Fareston), and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin, and pharmaceutically acceptable salts, acids or derivatives of any. . .

DETD . . . fibrosis), gluten sensitive enteropathy, dense deposit disease, chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, **cardiotomy**

syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulamatous, degenerative, and atrophic disorders) and other disorders such as. . .

DETD . . . characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), **cardiotomy** syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis. . .

DETD . . . and/or stroke, traumatic brain injury, neurodegenerative disorders (such as, e.g., Parkinson's disease and Alzheimer's disease), AIDS-related dementia, and prion disease); **cardiovascular** disorders (such as, e.g., atherosclerosis, myocarditis, **cardiovascular** disease, and **cardiopulmonary** bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (such as, e.g., chronic. . .

DETD . . . include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, **cardiac** tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma,. . .

DETD . . . and/or TNF epsilon polypeptides or polynucleotides encoding TNF delta and/or TNF epsilon of the invention may be used to treat **cardiovascular** disorders, including peripheral artery disease, such as limb ischemia.

DETD [0572] **Cardiovascular** disorders include **cardiovascular** abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart. . .

DETD [0573] **Cardiovascular** disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high **cardiac** output, low **cardiac** output, **cardiac** tamponade, endocarditis (including bacterial), heart aneurysm, **cardiac** arrest, congestive heart failure, congestive **cardiomyopathy**, paroxysmal dyspnea, **cardiac** edema, heart hypertrophy, congestive **cardiomyopathy**, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, **cardiovascular** pregnancy complications, Scimitar Syndrome, **cardiovascular** syphilis, and **cardiovascular** tuberculosis.

DETD [0576] Myocardial diseases include alcoholic **cardiomyopathy**, congestive **cardiomyopathy**, hypertrophic **cardiomyopathy** , aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive **cardiomyopathy**, Chagas **cardiomyopathy**, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

DETD [0578] **Cardiovascular** diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema,. . .

DETD [0582] Embolisms include air embolisms, amniotic fluid embolisms, **cholesterol** embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion,. . .

DETD . . . characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), **cardiotomy** syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis. . .

DETD . . . compositions of the invention in the treatment of hypertensive or large vessel diseases, including renal artery stenosis or occlusion and **cholesterol** emboli or renal emboli.

DETD . . . include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to, colon cancer, **cardiac** tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma,. . .

DETD . . . (e.g., HAV, HBV, HCV, etc.), Helicobacter pylori infection, invasive Staphylococcia, etc.), parasitic infection, nephritis, bone disease (e.g., osteoporosis), atherosclerosis, pain, **cardiovascular** disorders (e.g., neovascularization, hypovascularization or reduced circulation (e.g., ischemic disease (e.g., myocardial infarction, stroke, etc.)), AIDS, allergy, inflammation, neurodegenerative disease. . . multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, immune complex glomerulonephritis, autoimmune diabetes, autoimmune thrombocytopenic purpura, Grave's disease, Hashimoto's thyroiditis, etc.), **cardiomyopathy** (e.g., dilated **cardiomyopathy**), diabetes, diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy), influenza, asthma, psoriasis, glomerulonephritis, septic shock, and ulcerative colitis.

DETD . . . of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent **cholesterol**, the selected proportion being adjusted for the optimal TNF delta and/or TNF epsilon polypeptide therapy.

DETD . . . arteriosclerosis. Examples of such disorders include, but are not limited to, reperfusion damage (e.g., in the heart and/or brain) and **cardiac** hypertrophy.

DETD . . . deep vein thrombosis, pulmonary embolism, myocardial infarction, coronary artery disease (e.g., antibody -mediated coronary artery disease), thrombosis, graft reocclusion following **cardiovascular** surgery (e.g., coronary arterial bypass grafts, recurrent fetal loss, and recurrent **cardiovascular** thromboembolic events.

DETD . . . are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Pat. Nos. 5,693,622, 5,705,151, 5,580,859; Tabata H. et al., **Cardiovasc**. Res. 35:470-479 (1997); Chao J. et al., Pharmacol. Res. 35:517-522 (1997); Wolff J. A. Neuromuscul. Disord. 7:314-318 (1997); Schwartz B.. . .

L5 ANSWER 5 OF 15 USPATFULL
AN 2002:122443 USPATFULL
TI Method to determine TGF-.beta.
IN Grainger, David J., Cambridge, UNITED KINGDOM
Kemp, Paul R., Suffolk, UNITED KINGDOM
PA NeoRx Corporation, Seattle, WA, United States (U.S. corporation)
PI US 6395494 B1 20020528
AI US 1995-477393 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1994-242161, filed on 12 May 1994, now patented, Pat. No. US 5847007 Continuation-in-part of Ser. No. US 1994-241844, filed on 12 May 1994, now abandoned Continuation-in-part of Ser. No. US 1993-61714, filed on 13 May 1993, now abandoned

Continuation-in-part of Ser. No. US 1993-62451, filed on 13 May 1993, now abandoned
DT Utility
FS GRANTED
EXNAM Primary Examiner: Ponnaluri, Padmashri
LREP Schwegman, Lundberg, Woessner & Kluth, P.A.
CLMN Number of Claims: 74
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 4476
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##

wherein Z is C.dbd.O or a covalent bond; Y is H or O(C.sub.1-C.sub.4)alkyl, R.sup.1 and R.sup.2 are individually (C.sub.1-C.sub.4)alkyl or together with N are a saturated heterocyclic group, R.sup.3 is ethyl or chloroethyl, R.sup.4 is H or together with R.sup.3 is --CH.sub.2--CH.sub.2-- or --S--, R.sup.5 is I, O(C.sub.1-C.sub.4)alkyl or H and R.sup.6 is I, O(C.sub.1-C.sub.4)alkyl or H with the proviso that when R.sup.4, R.sup.5, and R.sup.6 are H, R.sup.3 is not ethyl; or a pharmaceutically acceptable salt thereof, effective to activate or stimulate production of TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compounds include idoxifene and salts thereof. Further provided is a method for identifying a compound that is a TGF-beta activator or production stimulator is provided. Another embodiment of the invention is an assay or kit to determine TGF-beta in vitro. Also provided is a therapeutic method comprising inhibiting smooth muscle cell proliferation associated with procedural vascular trauma employing the administration of tamoxifen or structural analogs thereof, including compounds of formula (I).

AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##

SUMM This invention relates generally to the prevention and treatment of **cardiovascular** pathologies. More specifically, a method for treating or preventing atherosclerosis is provided.

SUMM . . . in many patients with coronary artery disease. PTCA can relieve myocardial ischemia in patients with coronary artery disease by reducing **lumen** obstruction and improving coronary flow. The use of this surgical procedure has grown rapidly, with 39,000 procedures performed in 1983,. . .

SUMM In general, atherosclerosis is a **cardiovascular** disease in which the vessel wall is remodeled, compromising the **lumen** of the vessel. The atherosclerotic remodeling process involves accumulation of cells, both smooth muscle cells and monocyte/macrophage inflammatory cells, in. . .

SUMM Thus, a need exists for therapeutic methods and agents to treat **cardiovascular** pathologies, such as atherosclerosis and other conditions related to coronary artery disease.

SUMM A therapeutic method for preventing or treating a **cardiovascular** indication characterized by a decreased **lumen** diameter is provided. The method comprises administering to a mammal at risk of, or afflicted with, said **cardiovascular** indication, a cytostatic dose of a TGF-beta activator or production stimulator. The cytostatic dose is effective to activate or stimulate. . .

SUMM A therapeutic method is provided for treating or preventing **cardiovascular** pathologies, such as conditions selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke. The method comprises the. . .

SUMM A further embodiment of the invention is a method for preventing **cardiovascular** pathologies in a mammal at risk of such a condition. Such conditions include atherosclerosis, thrombosis, myocardial infarction, and stroke. The. . .

SUMM The delivery of TGF-beta activators or production stimulators to the **lumen** of a vessel via catheter, before, during or after angioplasty, is discussed in detail below. A stent or shunt useful. . .

SUMM In addition, methods for using TGF-beta to maintain and increase vessel **lumen** diameter in a diseased or injured mammalian vessel are described.

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats and these studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by the non-TMX analogs of formula (I), including the TMX analog **toremifene** and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD Also included within the scope of the term tamoxifen are the TMX structural analogs **toremifene** and raloxifene, metabolites or pharmaceutically acceptable salts thereof. Other "antisteroids" or "steroidal antagonists" can also be useful as TGF-beta activators. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . suppressing the pathological proliferation of the target cell population. The preferred dosage forms can also release compounds that increase vessel **lumen** area and blood flow, reducing the pathological alterations produced by this reduced blood supply.

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the tunica media smooth muscle cells lining the **lumen** to the dosage form. This dosage is determinable empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD In hypertension, there is increased thickness of the vessel media, with a consequent decrease in maximum **lumen** diameter, leading to increased vascular resistance. The increased thickness of the vessel media is due to growth of VSMC within. . .

DETD . . . proliferate in the intima. There they secrete extracellular matrix proteins and form a lipid-rich plaque that encroaches on the vascular **lumen**. This process is similar to, but slower than, the process that occurs following PTCA, leading to restenosis. Such inappropriate intimal. . .

DETD . . . diet, and also in apoE knockout mice fed a normal diet. Another animal model useful in screening agents is the **cholesterol**-fed Watanabe rabbit. Finally, small scale, pilot studies on candidate molecules are tested in patient groups with clinically significant coronary artery. . .

DETD . . . In addition, heparin coupled to agarose beads (Sigma Chemical Co., St. Louis, Mo.) was examined (see also Grainger et al., **Cardiovascular** Res. 27:223847, 1993).

DETD . . . whether the mice were fed a normal diet (Techlad, Madison, Wis.; 4% mouse/rat chow) or a lipid-rich diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium chelate.

DETD . . . by increasing TGF-.beta. activity, such as TMX (Grainger et al., Biochem. J., 294, 109 (1993)) and heparin (Grainger et al., **Cardiovas**. Res., 27, 2238 (1993)), inhibited the proliferation of EX but not ED cells.

DETD . . . in groups were weighed then fed ad libitum either normal mouse chow (ICN/Flow), or a high fat diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium cholate, or high fat diet containing 15 .mu.g TMX. . .

DETD . . . The column was eluted with buffer A at 0.4 ml/minute and fractions of 0.2 ml were collected and analyzed for **cholesterol**. **Cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) by adding 5 .mu.l from each column fraction to 200 .mu.l assay reagent in an ELISA. . . incubated at 37.degree. C. for 15 minutes and absorbance read at 492 nm. Serum for calibration containing 200 mg/dL total **cholesterol** (Sigma Diagnostics) was used to convert absorbance readings to **cholesterol** concentrations according to the manufacturer's instructions. The positions of elution of the major lipoprotein classes in mouse platelet-poor plasma under. . .

DETD Assays for Plasma Triglycerides, **Cholesterol** and Sex Hormones

DETD Total plasma triglycerides was measured by the UV end-point glycerol kinase enzymatic method (Sigma Diagnostics). Total plasma **cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) performed in ELISA plate wells as described above. 17-.beta.-estradiol was measured by a specific sandwich ELISA. .

DETD . . . on either a normal mouse chow (low fat diet), or a high fat chow containing 0.5% sodium cholate and 5% **cholesterol** (high fat diet), or high fat diet containing 15 .mu.g/g TMX (high TMX diet). The mice on the high TMX. . .

DETD . . .

Testosterone (ng/ml) Total 71 .+-. 2 92 .+-. 4* 79 .+-. 3** 83 .+-. 4***

Plasma Cholesterol (mg/dl) VLDL 4 30 38 42

Cholesterol (mg/dl) LDL 8 33 27 27

**cholesterol** (mg/dl) HDL- 58 27 11 14

**cholesterol** (mg/dl) Total 142 .+-. 15 109 .+-. 5* 111 .+-. 9 204 .+-. 36***

Triglycerides (mg/dl) SM-.alpha.- 146 .+-. 6 138 .+-. 8 168 .+-.. . .

DETD High or low TMX diets significantly lowered total plasma **cholesterol** by approximately 10% compared with mice on the high fat diet. Analysis of the lipoprotein profiles showed that for the mice on the low fat diet, most of the **cholesterol** was in the HDL fraction. After 3 months on the high fat diet, however, there was a marked increase in very low density lipoprotein (VLDL)

**cholesterol** of approximately 7-fold (Table 2) and LDL **cholesterol** (4-fold) whereas the amount of **cholesterol** in the HDL fraction was reduced by approximately 50% (Table 2). The high and low TMX diets had only small effects on the amount of **cholesterol** in VLDL or LDL, but further reduced the HDL **cholesterol** by approximately 50% (Table 2), accounting for most of the overall reduction in **cholesterol**. In contrast to the decrease in total plasma **cholesterol** concentration caused by the high TMX diet, there was an increase in plasma concentration of triglyceride (Table 2).

DETD . . . subsequently uptake of lipid by the activated cells when the mice are subjected to a high fat diet. Thus, the **cardiovascular** protective effect of TMX in mice may be due to elevation of TGF-.beta. in the artery wall which prevents VSMC. . . . TMX would prevent lipid lesion formation in apo(a) mice on a high fat diet. It is of interest that the **cardiovascular** protective effects of TMX against diet-induced lipid lesions in mice reported here were obtained at doses similar to those used. . .

L5 ANSWER 6 OF 15 USPATFULL
AN 2002:21845 USPATFULL
TI Compositions and methods for improved delivery of lipid regulating agents
IN Patel, Mahesh V., Salt Lake City, UT, UNITED STATES
Chen, Feng-Jing, Salt Lake City, UT, UNITED STATES
PI US 2002012680 A1 20020131
US 6451339 B2 20020917
AI US 2001-898553 A1 20010702 (9)
RLI Continuation of Ser. No. US 1999-258654, filed on 26 Feb 1999, GRANTED, Pat. No. US 6294192
DT Utility
FS APPLICATION
LREP REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
CLMN Number of Claims: 140
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 3604
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to triglyceride-free pharmaceutical compositions for delivery of hydrophobic therapeutic agents. Compositions of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compositions.

DETD . . . can be hydrophilic or hydrophobic. Preferred derivatives include the polyethylene glycol derivatives. A preferred hydrophobic surfactant in this class is **cholesterol**. A preferred hydrophilic surfactant in this class is PEG-24 **cholesterol** ether (Solulan C-24). Examples of surfactants of this class are shown in Table 10.

TABLE 10

Sterol and Sterol Derivative Surfactants

| COMPOUND | COMMERCIAL PRODUCT (Supplier) | HLB |
|---|---|---|
| **Cholesterol**, sitosterol, | | <10 |

lanosterol
PEG-24 **cholesterol** ether Solulan C-24 (Amerchol) >10
PEG-30 **cholesterol** Nikkol DHC (Nikko) >10
Phytosterol GENEROL series (Henkel) <10
PEG-25 phyto sterol Nikkol BPSH-25 (Nikko) >10
PEG-5 soya sterol Nikkol BPS-5 (Nikko) <10
PEG-10. . .
DETD . . . glycodeoxycholate
Sodium ursodeoxycholate
Sodium chenodeoxycholate
Sodium taurochenodeoxycholate
Sodium glyco cheno deoxycholate
Sodium cholylsarcosinate
Sodium N-methyl taurocholate
PHOSPHOLIPIDS
Egg/Soy lecithin [Epikuron .TM. (Lucas Meyer), Ovothin .TM. (Lucas Meyer)]
Lyso egg/soy lecithin
Hydroxylated lecithin
Lysophosphatidylcholine
**Cardiolipin**
Sphingomyelin
Phosphatidylcholine
Phosphatidyl ethanolamine
Phosphatidic acid
Phosphatidyl glycerol
Phosphatidyl serine
PHOSPHORIC ACID ESTERS
Diethanolammonium polyoxyethylene-10 oleyl ether phosphate
Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid. . .
DETD . . . mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, mofetil, mycophenolate, nilutamide, paclitaxel, procarbazine HCl, sirolimus, tacrolimus, tamoxifen citrate, teniposide, testolactone, topotecan HCl, and **toremifene** citrate;
DETD [0106] **cardiac** inotropic agents, such as amrinone, digitoxin, digoxin, enoximone, lanatoside C and medigoxin;
DETD . . . aqueous HEPES buffer rather than purified water. The resultant solution was spiked with radioactive active and perfused through isolated ileal **lumen** segment of known length and diameter. Loss of radioactivity from the lumenal side and appearance of radioactivity in the mesenteric. . .
DETD . . . flushed with saline maintained at 37.degree. C. Two 1.5 cm notched pieces of Teflon tubing were inserted into the intestinal **lumen** at each incision and tightened using 4-0 silk. A warm isotonic buffer was passed through the intestine using a 50-mL. . .
CLM What is claimed is:
. . . PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 **cholesterol**, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 **cholesterol**, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl. . .
. . . oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 **cholesterol**,

polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 **cholesterol**, sucrose monostearate, sucrose monolaurate, a poloxamer, or a mixture thereof.

. . . PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 **cholesterol**, a poloxamer, or a mixture thereof.

. . . C.sub.20 fatty acid; diglycerides of C.sub.6 to C.sub.20 fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; **cholesterol**; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan. . .

. . . agents, anti-muscarinic agents, anti-neoplastic agents, erectile dysfunction improvement agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents, sedatives, hypnotics, neuroleptics, .beta.-Blockers, **cardiac** inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine H,-receptor antagonists, keratolytics, lipid regulating agents, anti-anginal agents, nutritional agents, opioid. . .

. . . sumatriptan, zolmitriptan, naratiptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, pseudo-ephedrine, **toremifene**, atovaquone, metronidazole, furazolidone, paricalcitol, benzonatate, midazolam, zolpidem, gabapentin, zopiclone, digoxin, beclomethsone, budesonide, betamethasone, prednisolone, cisapride, cimetidine, loperamide, famotidine, lanosprazole, rabeprazole,. . .

. . . sumatriptan, zolmitriptan, naratiptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, pseudo-ephedrine, **toremifene**, atovaquone, metronidazole, furzolidone, paricalcitol, benzonatate, midazolam, zolpidem, gabapentin, zopiclone, digoxin, cisapride, cimetidine, loperamide, famotidine, lanosprazole, rabeprazole, nizatidine, omeprazole, citrizine, cinnarizine,. . .

. . . pizofetin, zolmitriptan, pseudo-ephedrine, naratiptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, **toremifene**, atovaquone, metronidazole, furzolidone, paricalcitol, benzonatate, cisapride, cimetidine, loperamide, famotidine, lanosprazole, rabeprazole, nizatidine, omeprazole, citrizine, cinnarizine, dexchlopheniramine, loratadine, clemastine, fexofenadine, chlorpheniramine,. . .

. . . PEG40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 **cholesterol**, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 **cholesterol**, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl. . .

. . . oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl

trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 **cholesterol**, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 **cholesterol**, sucrose monostearate, sucrose monolaurate, a poloxamer, or a mixture thereof.

. . . PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 **cholesterol**, a poloxamer, or a mixture thereof.

. . . C.sub.20 fatty acid; diglycerides of C.sub.6 to C.sub.20 fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; **cholesterol**; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan. . .

. . . agents, anti-muscarinic agents, anti-neoplastic agents, erectile dysfunction improvement agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents, sedatives, hypnotics, neuroleptics, .beta.-Blockers, **cardiac** inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine H,-receptor antagonists, keratolytics, lipid regulating agents, anti-anginal agents, nutritional agents, opioid. . .

. . . sumatriptan, zolmitriptan, naratiptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, ephedrine, **toremifene**, atovaquone, metronidazole, furazolidone, paricalcitol, benzonatate, midazolam, zolpidem, gabapentin, zopiclone, digoxin, beclomethsone, budesonide, betamethasone, prednisolone, cisapride, cimetidine, loperamide, famotidine, lanosprazole, rabeprazole,. . .

. . . sumatriptan, zolmitriptan, naratiptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, pseudo-ephedrine, **toremifene**, atovaquone, metronidazole, furzolidone, paricalcitol, benzonatate, midazolam, zolpidem, gabapentin, zopiclone, digoxin, cisapride, cimetidine, loperamide, famotidine, lanosprazole, rabeprazole, nizatidine, omeprazole, citrizine, cinnarizine,. . .

. . . pizofetin, zolmitriptan, pseudo-ephedrine, naratiptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, **toremifene**, atovaquone, metronidazole, furzolidone, paricalcitol, benzonatate, cisapride, cimetidine, loperamide, famotidine, lanosprazole, rabeprazole, nizatidine, omeprazole, citrizine, cinnarizine, dexchlopheniramine, loratadine, clemastine, fexofenadine, chlorpheniramine,. . .

L5 ANSWER 7 OF 15 USPATFULL
AN 2001:162866 USPATFULL
TI Triglyceride-free compositions and methods for improved delivery of hydrophobic therapeutic agents
IN Patel, Mahesh V., Salt Lake City, UT, United States
Chen, Feng-Jing, Salt Lake City, UT, United States
PA Lipocine, Inc., Salt Lake City, UT, United States (U.S. corporation)
PI US 6294192 B1 20010925
AI US 1999-258654 19990226 (9)

DT Utility
FS GRANTED
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Channavajjala, Lakshmi
LREP Reed, Dianne E.Reed & Associates
CLMN Number of Claims: 74
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 3094
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to triglyceride-free pharmaceutical compositions for delivery of hydrophobic therapeutic agents. Compositions of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compositions.
DETD . . . can be hydrophilic or hydrophobic. Preferred derivatives include the polyethylene glycol derivatives. A preferred hydrophobic surfactant in this class is **cholesterol**. A preferred hydrophilic surfactant in this class is PEG-24 **cholesterol** ether Solulan C-24). Exarnples of surfactants of this class are shown in Table 10.
DETD TABLE 10
Sterol and Sterol Derivative Surfactants

| COMPOUND | COMMERCIAL PRODUCT (Supplier) | HLB |
|---|---|---|
| **Cholesterol**, sitosterol, | | <10 |
| lanosterol | | |
| PEG-24 **cholesterol** ether | Solulan C-24 (Amerchol) | >10 |
| PEG-30 cholestanol | Nikkol DHC (Nikko) | >10 |
| Phytosterol | GENEROL series (Henkel) | <10 |
| PEG-25 phyto sterol | Nikkol BPSH-25 (Nikko) | >10 |

PEG-5. . .
DETD . . . glycodeoxycholate
Sodium ursodeoxycholate
Sodium chenodeoxycholate
Sodium taurochenodeoxycholate
Sodium glyco cheno deoxycholate
Sodium cholylsarcosinate
Sodium N-methyl taurocholate
PHOSPHOLIPIDS
Egg/Soy lecithin [Epikuron .TM. (Lucas Meyer), Ovothin .TM.] (Lucas Meyer)]
Lyso egg/soy lecithin
Hydroxylated lecithin
Lysophosphatidylcholine
**Cardiolipin**
Sphingomyelin
Phosphatidylcholine
Phosphatidyl ethanolamine
Phosphatidic acid
Phosphatidyl glycerol
Phosphatidyl serine
PHOSPHORIC ACID ESTERS
Diethanolammonium polyoxyethylene-10 oleyl ether phosphate
Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid. . .
DETD . . . mercaptopurine, methotrexate, mitomycin, mitotane,

mitoxantrone, mofetil mycophenolate, nilutamide, paclitaxel, procarbazine HCl, sirolimus, tacrolimus, tamoxifen citrate, teniposide, testolactone, topotecan HCl, and **toremifene** citrate;

DETD **cardiac** inotropic agents, such as amrinone, digitoxin, digoxin, enoximone, lanatoside C and medigoxin;

DETD . . . aqueous HEPES buffer rather than purified water. The resultant solution was spiked with radioactive active and perfused through isolated ideal **lumen** segment of known length and diameter. Loss of radioactivity from the lumenal side and appearance of radioactivity in the mesenteric. . .

DETD . . . flushed with saline maintained at 37.degree. C. Two 1.5 cm notched pieces of Teflon tubing were inserted into the intestinal **lumen** at each incision and tightened using 4-0 silk. A warm isotonic buffer was passed through the intestine using a 50-mL. . .

CLM What is claimed is:

. . . PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 capratelcaprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 **cholesterol**, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 **cholesterol**, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl. . .

. . . oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 **cholesterol**, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 **cholesterol**, sucrose monostearate, sucrose monolaurate, a poloxamer, or a mixture thereof.

. . . PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 **cholesterol**, a poloxamer, or a mixture thereof.

. . . C.sub.20 fatty acid; diglycerides of C.sub.6 to C.sub.20 fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; **cholesterol**; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan. . .

. . . agents, anti-muscarinic agents, anti-neoplastic agents, erectile dysfunction improvement agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents, sedatives, hypnotics, neuroleptics, .beta.-blockers, **cardiac** inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine H.sub.1 and H.sub.2 receptor antagonists, keratolytics, lipid regulating agents, anti-anginal agents,. . .

. . . sumatriptan, zolmitriptan, naratiptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, pseudo-ephedrine, **toremifene**, atovaquone, metronidazole, furazolidone, paricalcitol, benzonatate, mnidazolam, zolpidem, gabapentin, zopiclone, digoxin, beclomethsone, budesonide, betamethasone, prednisolone, cisapride, cimetidine, loperamide, famotidine, lanosprazole, rabeprazole,. . .

. . . sumatriptan, zolmitriptan, naratiptan, rizatriptan, aminogluthemide,

busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, pseudo-ephedrine, **toremifene**, atovaquone, metronidazole, furzolidone, paricalcitol, benzonatate, midazolam, zolpidem, gabapentin, zopiclone, digoxin, cisapride, cimetidine, loperamnide, famotidine, lanosprazole, rabeprazole, nizatidine, omeprazole, citrizine, cinnarizine,. . . . . pizofetin, zolmitriptan, pseudo-ephedrine, naratiptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecan, topotecan, nilutanide, bicalutanide, **toremifene**, atovaquone, metronidazole, fruzolidone, paricalcitol, benzonatate, cisapride, cimetidine, loperamide, famotidine, lanosprazole, rabeprazole, nizatidine, omeprazole, citrizine, cinnarizine, dexchlopheniramine, loratadine, clemastine, fexofenadine, chlorpheniramine,. . .

L5 ANSWER 8 OF 15 USPATFULL
AN 2001:112344 USPATFULL
TI Prevention and treatment of **cardiovascular** pathologies
IN Grainger, David J., Cambridge, United Kingdom
Metcalfe, James C., Cambridge, United Kingdom
Kunz, Lawrence L., Redmond, WA, United States
Schroff, Robert W., Edmonds, WA, United States
Weissberg, Peter L., Cambridge, United Kingdom
PA NeoRx Corporation, Seattle, WA, United States (U.S. corporation)
PI US 6262079 B1 20010717
AI US 1999-306606 19990506 (9)
RLI Continuation of Ser. No. US 1998-82643, filed on 21 May 1998 Division of Ser. No. US 1995-486334, filed on 7 Jun 1995, now patented, Pat. No. US 5770609 Continuation-in-part of Ser. No. US 1994-242161, filed on 12 May 1994, now patented, Pat. No. US 5847007 Continuation-in-part of Ser. No. US 1993-61714, filed on 13 May 1993, now abandoned Continuation-in-part of Ser. No. US 1994-241844, filed on 12 May 1994, now abandoned Continuation-in-part of Ser. No. US 1993-62451, filed on 13 May 1993, now abandoned Continuation-in-part of Ser. No. US 1993-11669, filed on 28 Jan 1993, now abandoned Continuation-in-part of Ser. No. WO 1992-US8220, filed on 25 Sep 1992
DT Utility
FS GRANTED
EXNAM Primary Examiner: Henley, III, Raymond
LREP Schwegman, Lundberg, Woessner & Kluth, P.A.
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 4234
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##

wherein Z is C.dbd.O or a covalent bond; Y is H or O(C.sub.1 -C.sub.4)alkyl, R.sup.1 and R.sup.2 are individually (C.sub.1 -C.sub.4)allyl or together with N are a saturated heterocyclic group, R.sup.3 is ethyl or chloroethyl, R.sup.4 is H or together with R.sup.3 is --CH.sub.2 --CH.sub.2 -- or --S--, R.sup.5 is I, O(C.sub.1 -C.sub.4)alkyl or H and R.sup.6 is I, O(C.sub.1 -C.sub.4)alkyl or H with the proviso that when R.sup.4 F R.sup.5, and R.sup.6 are H, R.sup.3 is not ethyl; or a pharmaceutically acceptable salt thereof, effective to activate or stimulate production of TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction,

and stroke is provided. Useful compounds include idoxifene and salts thereof. Further provided is a method for identifying a compound that is a TGF-beta activator or production stimulator is provided. Another embodiment of the invention is an assay or kit to determine TGF-beta in vitro. Also provided is a therapeutic method comprising inhibiting smooth muscle cell proliferation associated with procedural vascular trauma employing the administration of tamoxifen or structural analogs thereof, including compounds of formula (I).

TI Prevention and treatment of **cardiovascular** pathologies

AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##

SUMM This invention relates generally to the prevention and treatment of **cardiovascular** pathologies. More specifically, a method for treating or preventing atherosclerosis is provided.

SUMM . . . in many patients with coronary artery disease. PTCA can relieve myocardial ischemia in patients with coronary artery disease by reducing **lumen** obstruction and improving coronary flow. The use of this surgical procedure has grown rapidly, with 39,000 procedures performed in 1983,. . .

SUMM In general, atherosclerosis is a **cardiovascular** disease in which the vessel wall is remodeled, compromising the **lumen** of the vessel. The atherosclerotic remodeling process involves accumulation of cells, both smooth muscle cells and monocyte/macrophage inflammatory cells, in. . .

SUMM Thus, a need exists for therapeutic methods and agents to treat **cardiovascular** pathologies, such as atherosclerosis and other conditions related to coronary artery disease.

SUMM A therapeutic method for preventing or treating a **cardiovascular** indication characterized by a decreased **lumen** diameter is provided. The method comprises administering to a mammal at risk of, or afflicted with, said **cardiovascular** indication, a cytostatic dose of a TGF-beta activator or production -stimulator. The cytostatic dose is effective to activate or stimulate. . .

SUMM A therapeutic method is provided for treating or preventing **cardiovascular** pathologies, such as conditions selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke. The method comprises the. . .

SUMM A further embodiment of the invention is a method for preventing **cardiovascular** pathologies in a mammal at risk of such a condition. Such conditions include atherosclerosis, thrombosis, myocardial infarction, and stroke. The. . .

SUMM The delivery of TGF-beta activators or production stimulators to the **lumen** of a vessel via catheter, before, during or after angioplasty, is discussed in detail below. A stent or shunt useful. . .

SUMM In addition, methods for using TGF-beta to maintain and increase vessel **lumen** diameter in a diseased or injured mammalian vessel are described.

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats and these studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by the non-TMX analogs of formula (I), including the TMX analog **toremifene** and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD Also included within the scope of the term tamoxifen are the TMX structural analogs **toremifene** and raloxifene, metabolites or pharmaceutically acceptable salts thereof. Other "antisteroids" or "steroidal antagonists" can also be useful as TGF-beta activators. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . suppressing the pathological proliferation of the target cell population. The preferred dosage forms can also release compounds that increase vessel **lumen** area and blood flow, reducing the pathological alterations produced by this reduced blood supply.

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the tunica media smooth muscle cells lining the **lumen** to the dosage form This dosage is determinable empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD In hypertension, there is increased thickness of the vessel media, with a consequent decrease in maximum **lumen** diameter, leading to increased vascular resistance. The increased thickness of the vessel media is due to growth of VSMC within. . .

DETD . . . proliferate in the intima. There they secrete extracellular matrix proteins and form a lipid-rich plaque that encroaches on the vascular **lumen**. This process is similar to, but slower than, the process that occurs following PICA, leading to restenosis. Such inappropriate intimal. . .

DETD . . . diet, and also in apoE knockout mice fed a normal diet. Another animal model useful in screening agents is the **cholesterol**-fed Watanabe rabbit. Finally, small scale, pilot studies on candidate molecules are tested in patient groups with clinically significant coronary artery. . .

DETD . . . In addition, heparin coupled to agarose beads (Sigma Chemical Co., St. Louis, Mo.) was examined (see also Grainger et al., **Cardiovascular** Res. 27:2238-47, 1993).

DETD . . . whether the mice were fed a normal diet (Techlad, Madison, Wis.; 4% mouse/rat chow) or a lipid-rich diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium chelate.

DETD . . . by increasing TGF-.beta. activity, such as TMX (Grainger et al., Biochem. J., 294, 109 (1993)) and heparin (Grainger et al., **Cardiovas**. Res. 2, 2238 (1993)), inhibited the proliferation of EX but not ED cells.

DETD . . . in groups were weighed then fed ad libitum either normal mouse chow (ICN/Flow), or a high fat diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium cholate, or high fat diet containing 15 .mu.g TMX. . .

DETD . . . The column was eluted with buffer A at 0.4 ml/minute and fractions of 0.2 ml were collected and analyzed for **cholesterol**. **Cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) by adding S pi from each column fraction to 200 .mu.l assay reagent in an EUISA. . . incubated at 37.degree. C. for 15 minutes and absorbance read at 492 nm Serum for calibration containing 200 mg/dL total **cholesterol** (Sigma Diagnostics) was used to convert absorbance readings to **cholesterol** concentrations according to the manufacturer's instructions. The positions of elution of the major lipoprotein classes in mouse platelet-poor plasma under. . .

DETD Assays for Plasma Triglycerides, **Cholesterol** and Sex Hormones

DETD Total plasma triglycerides was measured by the UV end-point glycerol kinase enzymatic method (Sigma Diagnostics). Total plasma **cholesterol** was measured by the **cholesterol** oxidase

method (Sigma Diagnostics) performed in ELISA plate wells as described above. 17-.beta.-estradiol was measured by a specific sandwich EBLSA. . .

DETD . . . on either a normal mouse chow (low fat diet), or a high fat chow containing 0.5% sodium cholate and 5% **cholesterol** (high fat diet), or high fat diet containing 15 .mu.g TMX (high TMX diet). The mice on the high TMX. . .

DETD . . . .+-. 3 13 .+-. 5 11 .+-. 7

| | | | | |
|---|---|---|---|---|
| Testosterone (ng/ml) | | | | |
| Total Plasma **Cholesterol** (mg/dl) | 71 .+-. 2 | 92 .+-. 4* | 79 .+-. 3** | 83 .+-. 4*** |
| VLDL **Cholesterol** (mg/dl) | 4 | 30 | 38 | 42 |
| LDL **cholesterol** (mg/dl) | 8 | 33 | 27 | 27 |
| HDL- **cholesterol** (mg/dl) | 58 | 27 | 11 | 14 |
| Total Triglycerides (mg/dl) | 142 .+-. 15 | 109 .+-. 5* | 111 .+-. 9 | 204 .+-. 36*** |
| SM-.alpha.-actin | 146 .+-. 6 | 138 .+-. 8 | 168 .+-.. | . . |

DETD High or low TMX diets significantly lowered total plasma **cholesterol** by approximately 10% compared with mice on the high fat diet. Analysis of the lipoprotein profiles showed that for the mice on the low fat diet, most of the **cholesterol** was in the HDL fraction. After 3 months on the high fat diet, however, there was a marked increase in very low density lipoprotein (VLDL) **cholesterol** of approximately 7-fold (Table 2) and LDL **cholesterol** (4-fold) whereas the amount of **cholesterol** in the HDL fraction was reduced by approximately 50% (Table 2). The high and low TMX diets had only small effects on the amount of **cholesterol** in VLDL or LDL, but further reduced the HDL **cholesterol** by approximately 50% (Table 2), accounting for most of the overall reduction in **cholesterol**. In contrast to the decrease in total plasma **cholesterol** concentration caused by the high TMX diet, there was an increase in plasma concentration of triglyceride (Table 2).

DETD . . . subsequently uptake of lipid by the activated cells when the mice are subjected to a high fat diet. Thus, the **cardiovascular** protective effect of TV in mice may be due to elevation of TGF-.beta. in the artery wall which prevents VSMC. . . TMX would prevent lipid lesion formation in apo(a) mice on a high fat diet. It is of interest that the **cardiovascular** protective effects of TMX against diet-induced lipid lesions in mice reported here were obtained at doses similar to those used. . .

CLM What is claimed is:

2. The method of claim 1 wherein the structural analog of tamoxifen is droloxifene, idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, raloxifene, **toremifene**, or a pharmaceutically acceptable salt thereof.

18. The method of claim 17 wherein the compound is droloxifene, raloxifene, **toremifene**, tamoxifen, idoxifene, or a pharmaceutically acceptable salt thereof.

L5 ANSWER 9 OF 15 USPATFULL
AN 2001:97942 USPATFULL
TI Prevention and treatment of **cardiovascular** pathologies
IN Grainger, David J., Cambridge, United Kingdom
Metcalfe, James C., Cambridge, United Kingdom
Weissberg, Peter L., Cambridge, United Kingdom
PA NeoRx Corporation, Seattle, WA, United States (U.S. corporation)
PI US 6251920 B1 20010626
AI US 1998-82643 19980521 (9)
RLI Division of Ser. No. US 1995-486334, filed on 7 Jun 1995, now patented, Pat. No. US 5770609 Continuation-in-part of Ser. No. US 1994-242161, filed on 12 May 1994, now patented, Pat. No. US 5847007 Continuation-in-part of Ser. No. US 1993-61714, filed on 13 May 1993, now abandoned Continuation-in-part of Ser. No. US 1994-241844, filed on 12 May 1994, now abandoned Continuation-in-part of Ser. No. US 1993-62451, filed on 13 May 1993, now abandoned Continuation-in-part of Ser. No. US 1993-11669, filed on 28 Jan 1993, now abandoned Continuation-in-part of Ser. No. WO 1992-US8220, filed on 25 Sep 1992, now abandoned
DT Utility
FS GRANTED
EXNAM Primary Examiner: Henley, III, Patrick
LREP Schwegman, Lundberg, Woessner & Kluth, P.A.
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 4366
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##

wherein Z is C.dbd.O or a covalent bond; Y is H or O(C.sub.1 -C.sub.4)alkyl, R.sup.1 and R.sup.2 are individually (C.sub.1 -C.sub.4)alkyl or together with N are a saturated heterocyclic group, R.sup.3 is ethyl or chloroethyl, R.sup.4 is H or together with R.sup.3 is --CH.sub.2 --CH.sub.2 -- or --S--, R.sup.5 is I, O(C.sub.1 -C.sub.4)alkyl or H and R.sup.6 is I, O(C.sub.1 -C.sub.4)alkyl or H with the proviso that when R.sup.4, R.sup.5, and R.sup.6 are H, R.sup.3 is not ethyl; or a pharmaceutically acceptable salt thereof, effective to activate or stimulate production of TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compounds include idoxifene and salts thereof. Further provided is a method for identifying a compound that is a TGF-beta activator or production stimulator is provided. Another embodiment of the invention is an assay or kit to determine TGF-beta in vitro. Also provided is a therapeutic method comprising inhibiting smooth muscle cell proliferation associated with procedural vascular trauma employing the administration of tamoxifen or structural analogs thereof, including compounds of formula (I).
TI Prevention and treatment of **cardiovascular** pathologies
AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##
SUMM This invention relates generally to the prevention and treatment of **cardiovascular** pathologies. More specifically, a method for treating or preventing atherosclerosis is provided.
SUMM . . . in many patients with coronary artery disease. PTCA can relieve myocardial ischemia in patients with coronary artery disease by reducing **lumen** obstruction and improving coronary flow. The use of this surgical procedure has grown rapidly, with 39,000 procedures performed in 1983,. . .

SUMM In general, atherosclerosis is a **cardiovascular** disease in which the vessel wall is remodeled, compromising the **lumen** of the vessel. The atherosclerotic remodeling process involves accumulation of cells, both smooth muscle cells and monocyte/macrophage inflammatory cells, in. . .

SUMM Thus, a need exists for therapeutic methods and agents to treat **cardiovascular** pathologies, such as atherosclerosis and other conditions related to coronary artery disease.

SUMM A therapeutic method for preventing or treating a **cardiovascular** indication characterized by a decreased **lumen** diameter is provided. The method comprises administering to a mammal at risk of, or afflicted with, said **cardiovascular** indication, a cytostatic dose of a TGF-beta activator or production stimulator. The cytostatic dose is effective to activate or stimulate. . .

SUMM A therapeutic method is provided for treating or preventing **cardiovascular** pathologies, such as conditions selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke. The method comprises the. . .

SUMM A further embodiment of the invention is a method for preventing **cardiovascular** pathologies in a mammal at risk of such a condition. Such conditions include atherosclerosis, thrombosis, myocardial infarction, and stroke. The. . .

SUMM The delivery of TGF-beta activators or production stimulators to the **lumen** of a vessel via catheter, before, during or after angioplasty, is discussed in detail below. A stent or shunt useful. . .

SUMM In addition, methods for using TGF-beta to maintain and increase vessel **lumen** diameter in a diseased or injured mammalian vessel are described.

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats and these studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by the non-TMX analogs of formula (I), including the TMX analog **toremifene** and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD Also included within the scope of the term tamoxifen are the TMX structural analogs **toremifene** and raloxifene, metabolites or pharmaceutically acceptable salts thereof. Other "antisteroids" or "steroidal antagonists" can also be useful as TGF-beta activators. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . suppressing the pathological proliferation of the target cell population. The preferred dosage forms can also release compounds that increase vessel **lumen** area and blood flow, reducing the pathological alterations produced by this reduced blood supply.

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the tunica media smooth muscle cells lining the **lumen** to the dosage form. This dosage is determinable empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD In hypertension, there is increased thickness of the vessel media, with a consequent decrease in maximum **lumen** diameter, leading to increased vascular resistance. The increased thickness of the vessel

media is due to growth of VSMC within. . .

DETD . . . proliferate in the intima. There they secrete extracellular matrix proteins and form a lipid-rich plaque that encroaches on the vascular **lumen**. This process is similar to, but slower than, the process that occurs following PTCA, leading to restenosis. Such inappropriate intimal. . .

DETD . . . diet, and also in apoE knockout mice fed a normal diet. Another animal model useful in screening agents is the **cholesterol**-fed Watanabe rabbit. Finally, small scale, pilot studies on candidate molecules are tested in patient groups with clinically significant coronary artery. . .

DETD . . . In addition, heparin coupled to agarose beads (Sigma Chemical Co., St. Louis, Mo.) was examined (see also Grainger et al., **Cardiovascular** Res. 27:223847, 1993).

DETD . . . whether the mice were fed a normal diet (Techlad, Madison, Wis.; 4% mouse/rat chow) or a lipid-rich diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium chelate.

DETD . . . by increasing TGF-.beta. activity, such as TMX (Grainger et al., Biochem. J., 294, 109 (1993)) and heparin (Grainger et al., **Cardiovas**. Res., 27, 2238 (1993)), inhibited the proliferation of EX but not ED cells.

DETD . . . in groups were weighed then fed ad libitum either normal mouse chow (ICN/Flow), or a high fat diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium cholate, or high fat diet containing 15 .mu.g TMX. . .

DETD . . . The column was eluted with buffer A at 0.4 milminute and fractions of 0.2 ml were collected and analyzed for **cholesterol**. **Cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) by adding 5 .mu.l from each column fraction to 200 .mu.l assay reagent in an ELISA. . . incubated at 37.degree. C. for 15 minutes and absorbance read at 492 nm. Serum for calibration containing 200 mg/dL total **cholesterol** (Sigma Diagnostics) was used to convert absorbance readings to **cholesterol** concentrations according to the manufacturer's instructions. The positions of elution of the major lipoprotein classes in mouse platelet-poor plasma under. . .

DETD Assays for Plasma Triglycerides, **Cholesterol** and Sex Hormones Total plasma triglycerides was measured by the UV end-point glycerol kinase enzymatic method (Sigma Diagnostics). Total plasma **cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) performed in ELISA plate wells as described above. 17-.beta.-estradiol was measured by a specific sandwich ELISA. .

DETD . . . on either a normal mouse chow (low fat diet), or a high fat chow containing 0.5% sodium cholate and 5% **cholesterol** (high fat diet), or high fat diet containing 15 .mu.g/g TMX (high TMX diet). The mice on the high TMX. . .

DETD . . . .+-. 3 13 .+-. 5 11 .+-. 7

| | | | | |
|---|---|---|---|---|
| Testosterone (ng/ml) | | | | |
| Total Plasma **Cholesterol** (mg/dl) | 71 .+-. 2 | 92 .+-. 4* | 79 .+-. 3** | 83 .+-. 4*** |
| VLDL **Cholesterol** (mg/dl) | 4 | 30 | 38 | 42 |
| LDL **cholesterol** (mg/dl) | 8 | 33 | 27 | 27 |

| | | | | |
|---|---|---|---|---|
| HDL-**cholesterol** (mg/dl) | 58 | 27 | 11 | 14 |
| Total Triglycerides (mg/dl) | 142 .+-. 15 | 109 .+-. 5* | 111 .+-. 9 | 204 .+-. 36*** |
| SM-.alpha.-actin | 146 .+-. 6 | 138 .+-. 8 | 168 .+-.. | . . |

DETD High or low TVX diets significantly lowered total plasma **cholesterol** by approximately 10% compared with mice on the high fat diet. Analysis of the lipoprotein profiles showed that for the mice on the low fat diet, most of the **cholesterol** was in the HDL fraction. After 3 months on the high fat diet, however, there was a marked increase in very low density lipoprotein (VLDL) **cholesterol** of approximately 7-fold (Table 2) and LDL **cholesterol** (4-fold) whereas the amount of **cholesterol** in the HDL fraction was reduced by approximately 50% (Table 2). The high and low TMX diets had only small effects on the amount of **cholesterol** in VLDL or LDL, but further reduced the HDL **cholesterol** by approximately 50% (Table 2), accounting for most of the overall reduction in **cholesterol**. In contrast to the decrease in total plasma **cholesterol** concentration caused by the high TMX diet, there was an increase in plasma concentration of triglyceride (Table 2).

DETD . . . subsequently uptake of lipid by the activated cells when the mice are subjected to a high fat diet. Thus, the **cardiovascular** protective effect of TMX in mice may be due to elevation of TGF-.beta. in the artery wall which prevents VSMC. . . TMX would prevent lipid lesion formation in apo(a) mice on a high fat diet. It is of interest that the **cardiovascular** protective effects of TMX against diet-induced lipid lesions in mice reported here were obtained at doses similar to those used. . .

CLM What is claimed is:

9. The method of claim 1 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a pharmaceutically acceptable salt thereof.

19. A method comprising administering to a mammal at risk of a **cardiovascular** condition the following: an effective amount of a compound of formula (I): ##STR4## wherein Z is C.dbd.O or a covalent. . . ethyl; or a pharmaceutically acceptable salt thereof, wherein the amount is administered over time to the mammal to prevent a **cardiovascular** condition selected from the group consisting of thrombosis, myocardial infarction, and stroke.

27. The method of claim 19 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a pharmaceutically acceptable salt thereof.

32. The method of claim 31 wherein the compound of formula (I) is idoxifene, **toremifene** or a pharmaceutically acceptable salt thereof.

33. A therapeutic method for preventing or treating a **cardiovascular** indication characterized by a decreased **lumen** diameter comprising administering to a mammal at risk of or afflicted with said **cardiovascular** indication, a cytostatic dose of a therapeutic agent, wherein the cytostatic dose is effective to increase the level of TGF-beta. . .

36. The method of claim 34 wherein the therapeutic agent is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a

pharmaceutically acceptable salt thereof.

41. The method of claim 1, 19, 30 or 34 wherein the compound of formula (I) is **toremifene** or a pharmaceutically acceptable salt thereof.

L5 ANSWER 10 OF 15 USPATFULL
AN 2001:33286 USPATFULL
TI Prevention and treatment of **cardiovascular** pathologies with tamoxifen analogues
IN Grainger, David J., Cambridge, United Kingdom
Metcalfe, James C., Cambridge, United Kingdom
Kunz, Lawrence L., Redmond, WA, United States
Schroff, Robert W., Edmonds, WA, United States
PA NeoRx Corporation, Seattle, WA, United States (U.S. corporation)
PI US 6197789 B1 20010306
WO 9640098 19961219
AI US 1997-973570 19971205 (8)
WO 1996-US10211 19960607
19980908 PCT 371 date
19980908 PCT 102(e) date
RLI Continuation-in-part of Ser. No. US 1995-478936, filed on 7 Jun 1995, now abandoned Continuation-in-part of Ser. No. US 1995-476735, filed on 7 Jun 1995, now patented, Pat. No. US 5595722 Continuation-in-part of Ser. No. US 1995-477393, filed on 7 Jun 1995 Continuation-in-part of Ser. No. US 1995-486334, filed on 7 Jun 1995, now patented, Pat. No. US 5770609
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Schwegman, Lundberg, Woessner & Kluth, P.A.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 4577
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1##

wherein Z is C.dbd.O or a covalent bond; Y is H or O(C.sub.1 -C.sub.4)alkyl, R.sup.1 and R.sup.2 are individually (C.sub.1 -C.sub.4)alkyl or together with N are a saturated heterocyclic group, R.sup.3 is ethyl or chloroethyl, R.sup.4 is H, R.sup.5 is I, O(C.sub.1 -C.sub.4)alkyl or H and R.sup.6 is I, O(C.sub.1 -C.sub.4)alkyl or H with the proviso that when R.sup.4, R.sup.5, and R.sup.6 are H, R.sup.3 is not ethyl; or a pharmaceutically acceptable salt thereof, effective to elevate the level of TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compounds include idoxifene, **toremifene** or salts thereof. Further provided is a method for identifying an agent that elevates the level of TGF-beta. Another embodiment of the invention is an assay or kit to determine TGF-beta in vitro. Also provided is a therapeutic method comprising inhibiting smooth muscle cell proliferation associated with procedural vascular trauma employing the administration of tamoxifen or structural analogs thereof, including compounds of formula (I).
TI Prevention and treatment of **cardiovascular** pathologies with tamoxifen analogues
AB A method for treating or preventing **cardiovascular** pathologies

by administering a compound of the formula (I): ##STR1##

AB . . . TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compounds include idoxifene, **toremifene** or salts thereof. Further provided is a method for identifying an agent that elevates the level of TGF-beta. Another embodiment. . .

SUMM This invention relates generally to the prevention and treatment of **cardiovascular** pathologies. More specifically, a method for treating or preventing atherosclerosis is provided.

SUMM . . . in many patients with coronary artery disease. PTCA can relieve myocardial ischemia in patients with coronary artery disease by reducing **lumen** obstruction and improving coronary flow. The use of this surgical procedure has grown rapidly, with 39,000 procedures performed in 1983,. . .

SUMM In general, atherosclerosis is a **cardiovascular** disease in which the vessel wall is remodeled, compromising the **lumen** of the vessel. The atherosclerotic remodeling process involves accumulation of cells, both smooth muscle cells and monocyte/macrophage inflammatory cells, in. . .

SUMM Thus, a need exists for therapeutic methods and agents to treat **cardiovascular** pathologies, such as atherosclerosis and other conditions related to coronary artery disease.

SUMM A therapeutic method for preventing or treating a **cardiovascular** or vascular indication characterized by a decreased **lumen** diameter is provided. The method comprises administering to a mammal at risk of, or afflicted with, said **cardiovascular** indication, a cytostatic dose of a therapeutic agent that elevates the level of TGF-beta, such as a compound of formula. . .

SUMM A therapeutic method is provided for treating or preventing **cardiovascular** pathologies, such as conditions selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke. The method comprises the. . .

SUMM A further embodiment of the invention is a method for preventing **cardiovascular** pathologies in a mammal at risk of such a condition. Such conditions include atherosclerosis, thrombosis, myocardial infarction, and stroke. The. . .

SUMM The delivery of an agent that elevates the level of TGF-beta, e.g., TGF-beta activators or production stimulators, to the **lumen** of a vessel via catheter, before, during or after angioplasty, is discussed in detail below. A stent or shunt useful. . .

SUMM In addition, methods for using TGF-beta to maintain and increase vessel **lumen** diameter in a diseased or injured mammalian vessel are described.

SUMM . . . the proliferation of vascular tissue. A preferred embodiment of the invention includes the administration of idoxifene, 3-iodotamoxifen, 4-iodotamoxifen, raloxifene, droloxifene, **toremifene**, or a pharmaceutically acceptable salt thereof.

DRWD FIG. 4 depicts the association of TGF-beta with different lipoprotein classes. Profile of lipoprotein particle elution measured as total **cholesterol** (..... ) and TGF-beta elution (open circles) following separation of the lipoprotein fraction (d<1.215 g/cm.sup.3) by gel filtration chromatography. The. . .

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats and these studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by

the non-TMX analogs of formula (I), including the TMX analog **toremifene** and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD Also included within the scope of the term tamoxifen are the TMX structural analogs **toremifene** and raloxifene, metabolites or pharmaceutically acceptable salts thereof. Other "antisteroids" or "steroidal antagonists" can also be useful as agents that. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . suppressing the pathological proliferation of the target cell population. The preferred dosage forms can also release compounds that increase vessel **lumen** area and blood flow, reducing the pathological alterations produced by this reduced blood supply.

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the tunica media smooth muscle cells lining the **lumen** to the dosage form. This dosage is determinable empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD In hypertension, there is increased thickness of the vessel media, with a consequent decrease in maximum **lumen** diameter, leading to increased vascular resistance. The increased thickness of the vessel media is due to growth of VSMC within. . .

DETD . . . proliferate in the intima. There they secrete extracellular matrix proteins and form a lipid-rich plaque that encroaches on the vascular **lumen**. This process is similar to, but slower than, the process that occurs following PTCA, leading to restenosis. Such inappropriate intimal. . .

DETD . . . diet, and also in apoE knockout mice fed a normal diet. Another animal model useful in screening agents is the **cholesterol**-fed Watanabe rabbit. Finally, small scale, pilot studies on candidate molecules are tested in patient groups with clinically significant coronary artery. . .

DETD . . . In addition, heparin coupled to agarose beads (Sigma Chemical Co., St. Louis, Mo.) was examined (see also Grainger et al., **Cardiovascular** Res. 27:2238-47, 1993).

DETD . . . whether the mice were fed a normal diet (Techlad, Madison, Wis.; 4% mouse/rat chow) or a lipid-rich diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium chelate.

DETD . . . by increasing TGF-.beta. activity, such as TMX (Grainger et al., Biochem. J., 294, 109 (1993)) and heparin (Grainger et al., **Cardiovas**. Res., 27, 2238 (1993)), inhibited the proliferation of EX but not ED cells.

DETD . . . in groups were weighed then fed ad libitum either normal mouse chow (ICN/Flow), or a high fat diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium cholate, or high fat diet containing 15 .mu.g TMX. . .

DETD . . . The column was eluted with buffer A at 0.4 ml/minute and fractions of 0.2 ml were collected and analyzed for **cholesterol**. **Cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) by adding 5 .mu.l from each column fraction to 200 .mu.l assay reagent in an ELISA. . . incubated at 37.degree. C. for 15 minutes and absorbance read at 492 nm. Serum for calibration containing 200 mg/dL total **cholesterol** (Sigma Diagnostics) was used to convert absorbance readings to **cholesterol** concentrations according to the manufacturer's instructions. The positions of elution of the major lipoprotein classes in mouse platelet-poor plasma under. . .

DETD Assays for Plasma Triglycerides, **Cholesterol** and Sex Hormones

DETD Total plasma triglycerides was measured by the UV end-point glycerol kinase enzymatic method (Sigma Diagnostics). Total plasma **cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) performed in ELISA plate wells as described above. 17-.beta.-estradiol was measured by a specific sandwich ELISA. . .

DETD . . . on either a normal mouse chow (low fat diet), or a high fat chow containing 0.5% sodium cholate and 5% **cholesterol** (high fat diet), or high fat diet containing 15 .mu.g/g TMX (high TMX diet). The mice on the high TMX. . .

DETD . . . .+-. 3 13 .+-. 5 11 .+-. 7

Testosterone (ng/ml)

Total Plasma 71 .+-. 2 92 .+-. 4* 79 .+-. 3** 83 .+-. 4***

**Cholesterol** (mg/dl)

VLDL 4 30 38 42

**Cholesterol** (mg/dl)

LDL 8 33 27 27

**cholesterol** (mg/dl)

HDL- 58 27 11 14

**cholesterol** (mg/dl)

Total Triglycerides (mg/dl) 142 .+-. 15 109 .+-. 5* 111 .+-. 9 204 .+-. 36***

SM-.alpha.-actin 146 .+-. 6 138 .+-. 8 168 .+-.. . .

DETD High or low TMX diets significantly lowered total plasma **cholesterol** by approximately 10% compared with mice on the high fat diet. Analysis of the lipoprotein profiles showed that for the mice on the low fat diet, most of the **cholesterol** was in the HDL fraction. After 3 months on the high fat diet, however, there was a marked increase in very low density lipoprotein (VLDL) **cholesterol** of approximately 7-fold (Table 2) and LDL **cholesterol** (4-fold) whereas the amount of **cholesterol** in the HDL fraction was reduced by approximately 50% (Table 2). The high and low TMX diets had only small effects on the amount of **cholesterol** in VLDL or LDL, but further reduced the HDL **cholesterol** by approximately 50% (Table 2), accounting for most of the overall reduction in **cholesterol**. In contrast to the decrease in total plasma **cholesterol** concentration caused by the high TMX diet, there was an increase in plasma concentration of triglyceride (Table 2).

DETD . . . subsequently uptake of lipid by the activated cells when the mice are subjected to a high fat diet. Thus, the **cardiovascular** protective effect of TMX in mice may be due to elevation of TGF-.beta. in the artery wall which prevents VSMC. . . TMX would prevent lipid lesion formation in apo(a) mice on a high fat diet. It is of interest that the **cardiovascular** protective effects of TMX against diet-induced lipid lesions in mice reported here were obtained at doses similar to those used. . .

DETD . . . manufacturer's instructions. The proportion of TGF-beta in the lipoprotein fraction is shown in Table 8 (% associated TGF-beta). The total **cholesterol** in each fraction was measured by the **cholesterol** oxidase enzymatic method (Sigma Diagnostics) as previously described in Grainger et al., Nat. Med. J., 1067 (1995). The **cholesterol** in fractions 0-9 was assumed to be VLDL, in

fractions 10-19 to be LDL, and in fractions 20-30 to be HDL, in accordance with the elution positions of the major apolipoproteins. Lipoprotein concentrations are reported as mM **cholesterol**.

DETD . . . ka for TGF-beta binding to R2X to a maximal value of 42.+-.6 ng/ml when lipoprotein equivalent to 3 mM total **cholesterol** was added (FIG. 3A). Values are the mean.+-.standard error of triplicate determinations. The concentration of lipoprotein (measured as total **cholesterol**) which half-maximally increased the apparent ka was approximately 1 mM. Thus, the TGF-beta associated with the lipoprotein particles has a. . .

DETD . . . caused a dose-dependent increase in the ID.sub.50 of TGF-beta. The ID.sub.50 was maximal at 0.52.+-.0.08 ng/ml when 3 mM total **cholesterol** was added. The concentration of lipoprotein which half-maximally increased the ID.sub.50 was approximately 0.8 mM. Therefore, TGF-beta associated with lipoprotein. . .

DETD . . . the lipoprotein-associated TGF-beta eluted with a tightly defined subfraction of the HDL particles, with the smallest size of all the **cholesterol**-containing lipoprotein particles. The remaining 12% of the lipoprotein-associated TGF-beta was distributed among the VLDL and LDL fractions. This pattern of. . .

DETD Individual K was a diabetic patient with hypertriglyceridaemia, and >50% of the total plasma **cholesterol** was present in the largest triglyceride-rich lipoprotein particles (FIG. 4C). This individual had 78% of the plasma TGF-beta associated with. . .

DETD . . . TGF-beta associates with a subfraction of HDL particles which vary very little in size and which are among the smallest **cholesterol**-containing lipoproteins present in plasma. Additionally, TGF-beta can associate with both the triglyceride-rich LDL and VLDL particles, which can contain the. . .

CLM What is claimed is:

2. The method of claim 1 wherein the structural analog of tamoxifen is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, raloxifene, droloxifene, **toremifene**, or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 wherein the analog is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, droloxifene, **toremifene**, or a pharmaceutically acceptable salt thereof.

. . . kit comprising, separately packaged, a catheter adapted for the local delivery of a therapeutic agent to a site in the **lumen** of a mammalian vessel and a unit dosage of a therapeutic agent of formula (I): ##STR3## wherein Z is C.dbd.O. . .

6. The kit of claim 5 wherein the therapeutic agent of formula (I) is idoxifene, **toremifene**, or a pharmaceutically acceptable salt thereof.

. . . kit comprising, separately packaged, a catheter adapted for the local delivery of a therapeutic agent to a site in the **lumen** of a mammalian vessel and a unit dosage of droloxifene and pharmaceutically acceptable salts thereof, wherein the unit dosage is. . .

11. The kit of claim 5 wherein the agent is **toremifene**, or a pharmaceutically acceptable salt thereof.

L5 ANSWER 11 OF 15 USPATFULL
AN 2000:128378 USPATFULL
TI Estrogen agonist/antagonists treatment of atherosclerosis
IN Aiello, Robert J., Waterford, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 6124346 20000926

AI US 1999-407190 19990928 (9)
RLI Continuation of Ser. No. US 1997-955062, filed on 21 Oct 1997
PRAI US 1996-31275P 19961115 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Richardson, Peter C., Benson, Gregg C., Collier, Steven W.
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 583
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of treating atherosclerosis, independent of lipid lowering, in mammals, including humans, in need of treatment by inhibiting progression of an atherogenic lesion or by stabilizing plaque. Such lesion progression inhibition or plaque stabilization is preferably achieved by directly inhibiting chemokine expression leading to excessive inflammatory cell recruitment by administering certain estrogen agonist/antagonists.

SUMM . . . 500,000 deaths in the United States alone. Coronary artery stenosis and the number of diseased vessels are accepted markers of **cardiac** morbidity and mortality. The rupture of unstable atherosclerotic plaques contributes to nearly 75% of all myocardial infarctions and strokes. However,. . .

SUMM Also, Wiseman, et al. Biochem. Pharm. 45, No. 9, 1851 (1993) have described the role of lipid peroxidation in **cardiovascular** injury and the development of atherosclerosis. In addition, Wiseman et al. Cancer Letters 66, 61 (1992) have disclosed that droloxifene. . .

SUMM The preferred estrogen agonist/antagonists are tamoxifen, 4-hydroxy tamoxifen, raloxifene, **toremifene**, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol and {4-[2-(2-Aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone and pharmaceutically acceptably salts thereof.

DETD Another preferred estrogen agonist/antagonist is **toremifene**: (ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. Pat. No. 4,996,225 (the disclosure of which is hereby incorporated. . .

DETD Fed a Western-type diet containing 21% fat and 0.15% **cholesterol** (% by weight) (Harlan Teklad, Madison, Wis., Cat.# TD 88137 TEKLAD) for 3 months prior to sacrifice.

DETD . . . to sacrifice. The animals are anesthetized and a whole blood sample is removed from each animal for analysis of plasma **cholesterol** and triglycerides. The mice are perfused in situ with PBS (via heart puncture in the left ventricle) for a short. . .

DETD . . . mice were fed an adjusted calories "Western-type" diet (Harlan Teklad, Madison, Wis., Cat.# TD 88137, containing 21% fat and 0.15% **cholesterol** by weight). At weaning (age 28 days), female mice were bilaterally ovariectomized (OVX) or sham operated through a one centimeter. . .

DETD . . . up from the base of the heart, the sinus began at the first appearance of the valve cusps dividing the **lumen** into three distinct regions. In this region, the aortic wall is bulging and irregular. The sinus region ends and the valve region begins when the valve cusps no longer divide the **lumen** and the wall appears more rounded and distinct. The valve began at the end of the sinus and continued until. . .

DETD . . . lesion size per section or as the percent of the total cross sectional vessel wall area (normal+diseased area/section, excluding the

**lumen**) stained with Oil red O. For each animal, the average of 12 to 16 sections was determined and data are. . .

DETD Total plasma **cholesterol** and triglycerides were measured using calorimetric methods with commercially available kits (Wako and Boehrringer-Mannheim).

DETD . . . data demonstrates the reduction in atherosclerotic lesion size for the estrogen agonist {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone. Importantly, this occurred without a reduction in **cholesterol** as the **cholesterol** lowering activity of the estrogen agonist was not observed in this experiment, either because the compound was administered subcutaneously rather. . .

DETD TABLE

{4-[2-(2-Aza-bicyclo[2.2.1]hept-2-yl)-ethoxyl]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone Reduces Lesion Size in OVX apoE-Deficient Mice Without Affecting Plasma Lipids or Uterine Weight

| Group | N | Total **Cholesterol** (mg/dl) | Tri-glycerides (mg/dl) | Uterine WT (gm) | Aortic Valve Lesion area (%) |
|---|---|---|---|---|---|
| Placebo | 15 | 929 .+-. 315 | 96 .+-. 24 | 37 .+-. 39 | 33.4. . . |

CLM What is claimed is:

. . . comprising: administering to said mammal an effective amount of a member selected from the group consisting of 4-hydroxy tamoxifen, raloxifene, **toremifene**, centchroman, idoxifene, 6-(4-Hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol or {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, or the pharmaceutically acceptable salts thereof, and combinations thereof.

7. A method as recited in claim 1 wherein the compound is **toremifene**.

12. A method of inhibiting an inflammation process in a mammal, comprising: administering to said mammal an effective amount of a member selected from the group consisting of 4-hydroxy tamoxifen, raloxifene, **toremifene**, centchroman, idoxifene, 6-(4-Hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol or {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, or the pharmaceutically acceptable salts thereof, and combinations thereof.

18. A method as recited in claim 12 wherein the compound is **toremifene**.

L5 ANSWER 12 OF 15 USPATFULL

AN 2000:121554 USPATFULL

TI Compounds and therapies for the prevention of vascular and non-vascular pathologies

IN Grainger, David J., Cambridge, United Kingdom
Metcalfe, James C., Cambridge, United Kingdom

Kasina, Sudhakar, Mercer Island, WA, United States
PA NeoRx Corporation, Seattle, WA, United States (U.S. corporation)
PI US 6117911 20000912
AI US 1998-57323 19980409 (9)
PRAI US 1997-43852P 19970411 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Lambkin, Deborah C.
LREP Schwegman, Lundberg, Woessner & Kluth, P.A.
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 4129
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a method of treating a mammal having, or at risk of, an indication associated with a TGF-beta deficiency comprising administering one or more agents that is effective to elevate the level of TGF-beta. The invention also provides novel compounds that elevate TGF-beta levels, as well as pharmaceutical compositions comprising compounds that elevate TGF-beta levels, and methods for detecting diseases associated with endothelial cell activation.

SUMM . . . (Grainger et al., Biochem. J., 294 109 (1993)) and aspirin (Grainger et al., Nat. Med., 1, 74 (1995)), can exhibit **cardioprotective** effects. However, the positive **cardioprotective** effects of these agents may be counterindicated by their potential side effects. TMX can cause liver carcinogenicity in rats, has. . .

SUMM . . . lupus erythematosus, and other auto-immune disorders. Such agents may also be useful to promote wound healing and to lower serum **cholesterol** levels.

SUMM . . . an aspirinate that elevates the level of TGF-beta in said mammal so as to inhibit or reduce diminution in vessel **lumen** diameter. Preferably, the levels of active TGF-beta are elevated after administration of the aspirinate.

SUMM . . . of TGF-beta, preferably the level of active TGF-beta, in said mammal. Preferably, the administration inhibits or reduces diminution in vessel **lumen** diameter. The inhibition or reduction in diminution in vessel **lumen** diameter preferentially occurs at a site in a vessel where the vascular indication is, or is likely to be, manifested.. . . to bind to, or is capable of binding to, the TGF-beta receptor. This combination therapy can yield a significantly greater **cardiovascular** efficacy than would be expected from the administration of either agent singly. The therapeutic agents can act in a synergistic,. . .

SUMM . . . receptors. Thus, the agents of the invention are administered in a combined amount that prevents or inhibits diminution in vessel **lumen** diameter at, or near, a site or potential site of atherosclerotic lesion formation or development. A preferred first therapeutic agent. . .

SUMM The invention also provides a method to inhibit diminution in mammalian vessel **lumen** diameter. The method comprises administering to a mammal in need of said therapy, an amount of a first therapeutic agent. . . a second therapeutic agent effective to maintain or elevate the level of TGF-beta, so as to inhibit or reduce vessel **lumen** diminution. The inhibition or reduction in diminution in vessel **lumen** diameter preferentially occurs at a site in a vessel where the diminution is or is likely to be manifested. The. . .

SUMM . . . to the TGF-beta receptors. Agents useful to increase the level of latent TGF-beta include, but are not limited to, idoxifene, **toremifene**, raloxifene, droloxifene, ethynyl estradiol,

diethylstibestrol, 1,25 dihydroxy-vitamin D3, retinoic acid and ligand pharmaceutical analogs thereof (Mukherjee et al. Nature, 1997,. . .

SUMM . . . enclosing, separately packaged, at least one device adapted for the delivery of a therapeutic agent to a site in the **lumen** of a mammalian vessel and at least one unit dosage form of a first therapeutic agent and one unit dosage. . .

DRWD FIG. 3 depicts the association of TGF-beta with different lipoprotein classes. Profile of lipoprotein particle elution measured as total **cholesterol** ( . . . ) and TGF-beta elution (open circles) following separation of the lipoprotein fraction (d<1.215 g/cm.sup.3) by gel. . .

DRWD FIG. 8 depicts the effect of tamoxifen (TMX) on various **cardiovascular** risk factors. A) Lipoprotein(a) amounts. B) Proportion of TGF-beta associated with the lipoprotein fraction.

DETD . . . pharmaceutically acceptable salt thereof, or a combination thereof, in an amount effective to inhibit or reduce the diminution in vessel **lumen** diameter in a diseased, e.g., atherosclerotic, or traumatized, e.g., due to stent placement, vessel.

DETD For the prevention of vessel **lumen** diminution associated with procedural vascular trauma, the therapeutic agent can be administered before, during or after the procedure, or any. . .

DETD . . . fatty acid, wherein said amount is effective to increase the level of TGF-beta so as to inhibit or reduce vessel **lumen** diameter diminution. The invention also provides for the administration of at least two therapeutic agents which together are effective to elevate the levels of TGF-beta in a mammal so as to inhibit or reduce vessel **lumen** diameter diminution. The invention also provides combination therapies to maintain elevated levels of TGF-beta in a mammal which is not. . .

DETD . . . amount effective to increase TGF-beta levels. The increase in TGF-beta levels, in turn, inhibits or reduces the diminution in vessel **lumen** diameter in a diseased, e.g., atherosclerotic, or traumatized, e.g., due to stent placement, vessel. The increase in TGF-beta levels can. . .

DETD . . . kit comprising a catheter adapted for the local delivery of at least one therapeutic agent to a site in the **lumen** of a mammalian vessel, along with instruction means directing its use in accord with the present invention. Preferably, the therapeutic. . .

DETD . . . second agents may be introduced via discrete lumens of a catheter, or mixed together prior to introduction into a single **lumen** of a catheter. If the unit dosage forms are introduced into discrete lumens of a catheter, the delivery of the agents to the vessel can occur simultaneously or sequentially. Moreover, a single **lumen** catheter may be employed to deliver a unit dosage form of one agent, followed by the reloading of the **lumen** with another agent and delivery of the other agent to the **lumen** of the vessel. Either or both unit dosages can act to reduce the diminution in vessel **lumen** diameter at the target site.

DETD "**Cholesterol** lowering agents" include agents which are useful for lowering serum **cholesterol** such as for example bile acid sequestering resins (e.g. colestipol hydrochloride or cholestyramine), fibric acid derivatives (e.g. clofibrate, fenofibrate, or. . .

DETD . . . as well as other auto-immune disorders. Non-vascular indications also include the promotion of wound healing and the lowering of serum **cholesterol** levels.

DETD . . . carbon atom from the methyl end of the fatty acid chain. These fatty acids have been proposed to yield significant **cardiovascular** protection (Burr et al., Lancet, 221, 757 (1989)). Omega-3 fatty acids include 5, 8, 11, 14, 17-eicosapentaenoic acid and docosahexaenoic. . .

DETD "Vascular indication" includes, but is not limited to, a **cardiovascular** disease, e.g., atherosclerosis, thrombosis, myocardial infarction, and stroke, or a **cardiovascular** condition, e.g., vessels subjected to trauma associated with interventional procedures ("procedural vascular trauma"), such as restenosis following angioplasty, placement of. . . term "vascular indication" is non-coronary vessel disease, such as arteriolosclerosis, small vessel disease, nephropathy, greater than normal levels of serum **cholesterol**, asthma, hypertension, emphysema and chronic obstructive pulmonary disease. "Vascular indication" does not include cancer, including smooth muscle cell carcinomas or. . .

DETD . . . of TGF-beta protein include, but are not limited to, moieties which affect the nuclear hormone receptor pathway (e.g., tamoxifen, idoxifene, **toremifene**, raloxifene, droloxifene and other anti-estrogen analogues of tamoxifen, ethynyl estradiol, diethylstilbestrol, other synthetic estrogen agonists and compounds disclosed in U.S.. . .

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats. These studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by the non-TMX analogs of formula (VI), including the TMX analog **toremifene**, and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD . . . TGF-beta activators or production stimulators or lead compounds, including other known stilbene-type antisteroids such as for example, cis- and trans-clomiphene, **toremifene**, centchroman, raloxifene, droloxifene, (1-[4-(2-dimethylaminoethoxy)phenyl]-1-(3-hydroxyphenyl)-2-phenyl-2-butene (see U.S. Pat. No. 5,384,332), 1-nitro-1-phenyl-2-(4-hydroxyphenyl or anisyl)-2-[4-(2-pyrrol-N-ylethoxy)-phenyl]ethylene(CN-55,945),trans-1,2-dimethyl-1,2-(4-hydroxyphenyl)ethylene(trans-dimethylstilboestrol), trans-diethylstilboestrol, and 1-nitro-1-phenyl-2-(4-hydroxyphenyl)-2-[4-(3-dimethylaminopropyloxy)phenyl-ethylene (GI680), metabolites or pharmaceutically acceptable. . .

DETD . . . expressing the human apo(a) transgene that are fed a high fat diet, apoE knockout mice fed a normal diet, or **cholesterol**-fed Watanabe rabbits.

DETD . . . a backing layer and a polymer matrix which has dispersed or dissolved therein a therapeutic agent effective for reducing vessel **lumen** diameter diminution, along with one or more skin permeation enhancers. The backing layer can be made of any suitable material. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . by polymeric endoluminal sealing. This technique uses a catheter to apply a polymeric implant to the interior surface of the **lumen**. The therapeutic agent incorporated into the biodegradable polymer implant is thereby released at the surgical site. This technique is described. . .

DETD . . . of an aspirinate effective to elevate the level of TGF-beta so as to inhibit or reduce the diminution of vessel **lumen** diameter. Specifically, the administration is effective to reduce or

prevent lipid accumulation by the vessel, to increase plaque stability of. . .

DETD A further aspect of the invention provides a therapeutic method for lowering serum **cholesterol**, comprising administering to a mammal in need of such therapy, an effective amount of an aspirinate.

DETD . . . a kit comprising, separately packaged, a device adapted for the local delivery of an agent to a site in the **lumen** of a vessel of a mammal, and at least one unit dosage form of an aspirinate, wherein the aspirinate is. . .

DETD . . . wherein said amount is effective to maintain or increase the level of TGF-beta so as to inhibit or reduce vessel **lumen** diameter diminution.

DETD . . . comprising, separately packaged, a device adapted for the local delivery of at least one agent to a site in the **lumen** of a mammalian vessel and at least one unit dosage of aspirin or an aspirinate and at least one unit. . .

DETD The total **cholesterol** in each fraction was measured by the **cholesterol** oxidase enzymatic method (Sigma Diagnostics) as previously described in Grainger et al., Nat. Med., 1, 1067 (1995). The **cholesterol** in fractions 0-9 was assumed to be VLDL, in fractions 10-19 to be LDL, and in fractions 20-30 to be HDL, in accordance with the elution positions of the major apolipoproteins. Lipoprotein concentrations are reported as mM **cholesterol**. For cell cultures studies, the lipoprotein fraction was subjected to extensive dialysis against serum-free DMEM, and the amount of TGF-beta. . .

DETD . . . ka for TGF-beta binding to R2X to a maximal value of 42.+-.6 ng/ml when lipoprotein equivalent to 3 mM total **cholesterol** was added (FIG. 2A; values are the mean.+-.standard error of triplicate determinations). The concentration of lipoprotein (measured as total **cholesterol**) which half-maximally increased the apparent ka was approximately 1 mM. Thus, TGF-beta which is associated with lipoprotein particles has a. . .

DETD . . . caused a dose-dependent increase in the ID.sub.50 of TGF-beta. The ID.sub.50 was maximal at 0.52.+-.0.08 ng/ml when 3 mM total **cholesterol** was added. The concentration of lipoprotein which half-maximally increased the ID.sub.50 was approximately 0.8 mM. Therefore, TGF-beta associated with lipoprotein. . .

DETD . . . the lipoprotein-associated TGF-beta eluted with a tightly defined subfraction of the HDL particles, with the smallest size of all the **cholesterol**-containing lipoprotein particles, The remaining 12% of the lipoprotein-associated TGF-beta was distributed among the VLDL and LDL fractions. This pattern of. . .

DETD Individual K was a diabetic patient with hypertriglyceridaemia, and >50% of the total plasma **cholesterol** was present in the largest triglyceride-rich lipoprotein particles (FIG. 3C). This individual had 78% of the plasma TGF-beta associated with. . .

DETD . . . TGF-beta associates with a subfraction of HDL particles which vary very little in size and which are among the smallest **cholesterol**-containing lipoproteins present in plasma. Additionally, TGF-beta can associate with both the triglyceride-rich LDL and VLDL particles (FIG. 10). Indeed, under. . .

DETD At the end of the four week supplementation period total plasma triglyceride concentrations were somewhat reduced although total plasma **cholesterol** was unaffected (FIG. 4; Table 2). Fish oil supplementation also markedly reduced TGF-beta association with the lipoprotein fraction. The mean. . .

DETD . . . TGF-beta but increases TGF-beta bioavailability by decreasing the lipoprotein sequestration of the TGF-beta. Such an effect would likely result in **cardioprotection** in individuals with adequate

production of latent and mature TGF-beta but limited ability to release TGF-beta from lipoprotein complexes.

DETD TABLE 2

| Time (weeks) | Total associated Fish oil supplementation | Total triglyceride (mM) | **cholesterol** (mM) | % TGF-beta |
|---|---|---|---|---|
| 0 | None | 1.43 .+-. 0.43 | 5.1 .+-. 1.2 | 19 .+-. 10 |

n = 32

4. . .

DETD . . . following dietary supplementation with fish oil. Total triglyceride concentration was measured by the glycerol kinase enzymatic method (Sigma Diagnostics). Total **cholesterol** and % associated TGF-beta were assayed as described in Example I. Values are mean.+-.standard error. *=p<0.01; paired Wilcoxon signed-rank test. . .

DETD Aspirin has been suggested to have **cardioprotective** effects and is now in widespread use by patients diagnosed with coronary atherosclerosis. It has been demonstrated to significantly reduce. . .

DETD A number of effects have been suggested to play a role in the **cardioprotective** benefits associated with chronic use of low-dose aspirin. Aspirin interferes with normal platelet function and increases the blood clotting time,. . . formation is the main cause of MI, the anti-platelet function of aspirin is thought to be important in mediating its **cardioprotective** effects. Moreover, since aspirin is a well-documented anti-inflammatory agent and atherosclerosis has an important inflammatory component, the anti-inflammatory action of aspirin could also contribute to **cardioprotection**.

DETD Consumption of red wine has been proposed to mediate **cardiovascular** protection, although the data supporting this proposal are still debated. To determine whether red wine, as opposed to white wine,. . .

DETD Total plasma triglyceride, total plasma **cholesterol**, HDL-**cholesterol**, LDL-**cholesterol** and VLDL-**cholesterol** were routinely assayed in all patients. Liver function tests (aspartate transaminase and lactate dehydrogenase) were also performed on samples prior. . .

DETD TABLE 3

| | Day 0 | Day 10 |
|---|---|---|
| Age (yrs) | 62.2 .+-. 1.5 | |
| Total plasma **cholesterol** (mM) | 6.31 .+-. 0.28 | 5.95 .+-. 0.29* |
| VLDL-**cholesterol** (mM) | 1.03 .+-. 0.14 | 0.84 .+-. 0.11* |
| LDL-**cholesterol** (mM) | 4.48 .+-. 0.27 | 4.16 .+-. 0.25 |
| HDL-**cholesterol** (mM) | 0.78 .+-. 0.03 | 0.77 .+-. 0.04 |
| Total plasma triglycerides (mM) | 2.79 .+-. 0.44 | 2.28 .+-. 0.35 |

Plasma (a +. . .

DETD Another **cardiovascular** risk factor which has been shown to influence TGF-beta activity is the lipoprotein profile, since TGF-beta can be sequestered into lipoprotein particles where it is biologically inactive. TMX has been reported to decrease plasma **cholesterol** and to increase the fraction of **cholesterol** in HDL particles. Consistent with these reports, total plasma **cholesterol** was decreased by 6% below baseline (p=0.04) after 10 days of TMX therapy. In

addition, **cholesterol** in the VLDL fraction was reduced (18% below baseline; p=0.04) but the concentration of LDL-**cholesterol** and HDL-**cholesterol** were both unchanged (Table 3). Total plasma triglyceride concentration was 18% lower after 10 days of TMX treatment, but the. . .

DETD Another disadvantage of aspirin as a **cardiovascular** agent, besides the fact that it is not a very potent TGF-beta elevating agent, is that it appears to be. . .

DETD . . . aspirin and fish oil, 8-week-old female apoE knockout mice were fed aspirin or fish oil, or both, to assess the **cardioprotective** effects of modulating different components of the TGF-beta pathway.

DETD . . . Dohme) at 400 .mu.g/kg/day (2 .mu.g/g food). Simvastatin is an inhibitor of the enzyme HMG-CoA reductase, the committed step in **cholesterol** biosynthesis. As a result, it has been shown to reduce the total plasma **cholesterol** concentration in man and in particular the concentration of **cholesterol** in the more triglyceride-rich particles (VLDL and LDL). If alterations in the lipid profile are responsible for the suppression of. . .

DETD . . . greater the inhibition of lesion development. This correlation provides powerful evidence supporting the role of TGF-beta activity in mediating the **cardioprotective** activity of both tamoxifen, and aspirin and fish oil.

DETD The effect of each treatment on the lipid profile of each group of mice was determined by measuring the **cholesterol** and triglyceride. Blood from a terminal bleed was collected in a polypropylene tube, allowed to clot at room temperature for. . . hours and then spun (1,000.times.g; 5 minutes). The serum supernatant was aliquoted and stored at -20.degree. C. until assayed. Total **cholesterol** and total triglycerides were determined for each mouse using the **cholesterol** oxidase and glycerol kinase UV end-point enzymatic methods respectively (Sigma Diagnostics). For determination of the lipoprotein profile, 100 .mu.l of. . . filtration FPLC chromatography on a Sepharose 6B column, and the elution positions of the lipoprotein particles were detected by measuring **cholesterol** (by the **cholesterol** oxidase enzymatic method) in each fraction. VLDL particles eluted in fractions 1-10, LDL in fractions 11-20 and HDL in fractions. . .

DETD Treatment of the mice with aspirin for three months had no effect on total plasma **cholesterol** or on the lipoprotein profile (Table 8). Mice treated with diets containing fish oil (with or without aspirin) had similar total plasma **cholesterol** and triglyceride concentrations to control mice, although there was a small reduction in the concentration of both VLDL-**cholesterol** (-16%) and LDL-**cholesterol** (-12%) and an increase in HDL-**cholesterol** (+10%). Consistent with the effects of dietary supplementation with fish oil in man, a decrease in **cholesterol**, primarily in the VLDL fraction, in apoE knockout mice treated with fish oil was observed.

DETD There was a significant reduction in total plasma **cholesterol** in apoE knockout mice treated with simvastatin (-27%; p<0.01; n=10; Students unpaired t-test). Much of this reduction occurred in the VLDL fraction (-14%) and LDL fraction (-41%), with an increase in HDL-**cholesterol**. In contrast, TMX lowered VLDL by seven fold and is a much more powerful lipid-lowering agent in the apo(E)-/- mouse. . .

DETD TABLE 9

---

Group A
Group B
Group C
Group D
Group E

Group F

| | | | | | | |
|---|---|---|---|---|---|---|
| Total **cholesterol** (mg/dl) | n.d. | 306 .+-. 31 | 282 .+-. 28 | 273 .+-. 19 | 266 .+-. 25 | 224 .+-. 29** |
| Total triglyceride (mg/dl) | n.d. | 302 .+-. 28 | 320 .+-. 19 | 308 .+-. 25 | 296 .+-. 33 | 266 .+-. 14** |
| VLDL-**cholesterol** (mg/dl) | n.d. | 184 | 179 | 157 | 151 | 158 |
| LDL-**cholesterol** (mg/dl) | n.d. | 92 | 89 | 91 | 88 | 54 |
| HDL-**cholesterol** (mg/dl) | n.d. | 30 | 26 | 32 | 33 | 35 |

**p < 0.001; MannWhitney U test
n.d. = not determined.
A single measurement. . .

DETD . . . formation. If low dose aspirin therapy and dietary supplementation with fish oil differ in their mechanism of action, then their **cardioprotective** effects would be expected to be additive. However, the results described hereinabove provide evidence that the combination of aspirin and. . . a markedly synergistic effect. Thus, a combination of low dose aspirin and fish oil therapy can be very useful in **cardiovascular** disease prevention. Moreover, because fish oil is not a very effective VLDL lowering agent, more powerful VLDL lowering agents, such as TMX, can be employed in combination therapies with aspirin, aspirinate salts to result in more beneficial **cardiovascular** effects.

DETD . . . transgenic mouse models of atherosclerosis (Grainger et al.). However, tamoxifen has a variety of other effects, including reducing total plasma **cholesterol** and inducing some weight loss, which may have contributed to the observed reduction in lesion development. As a result, it. . .

DETD . . . tissue and the subsequent damage or destruction of that tissue by chronic inflammation. Preferred ER/NFkB modulators include idoxifene, raloxifene, droloxifene, **toremifene**, and tamoxifen, as well as functional equivalents, analogs or derivatives thereof. These agents also inhibit or reduce TNF-alpha mediated NFkB. . .

DETD Effects of the Therapeutic Agents on **Cholesterol** Levels

DETD Twenty six patients with high **cholesterol** were administered simvastatin for 16 weeks. Blood was collected at six times points during the 16 weeks and analyzed for TGF-beta levels. While serum **cholesterol** levels were reduced in these patients, there was no effect on TGF-beta levels in any of the patients. In contrast,. . . the patients participating in a trial in which tamoxifen, a tamoxifen analog, or placebo, was administered, showed significant decreases in **cholesterol** levels. Therefore, a combination of one of the therapeutic agents of the invention and an agent which lowers serum **cholesterol** levels may exert a synergistic effect and thus, may be useful in the practice in the methods of the invention. Moreover, therapeutic agents of the invention alone may be useful to lower serum **cholesterol** levels.

CLM What is claimed is:

. . . (C.sub.1 -C.sub.6)alkanoyl; the compound is MER25; or a pharmaceutically acceptable salt thereof; provided the compound of formula VI is not **toremifene**, tamoxifen, monophenoltamoxifen, 4-hydroxytoremifene, clomifene, 4-hydroxytamoxifen, 3-hydroxytamoxifen, N-desmethyltamoxifen, cyanotamoxifen, N-desmethyltoremifene, monophenoltoremifene, or deaminotoremifene.

. . . benzyl, or (C.sub.1 -C.sub.6)alkanoyl; the compound is MER25; or a pharmaceutically acceptable salt thereof; provided that the compound is not **toremifene**, tamoxifen, 4-hydroxytamoxifen, 3-hydroxytamoxifen, 4-hydroxytoremifene or N-desmethyltoremifene.

8. A therapeutic method for lowering serum **cholesterol** comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula VI: ##STR24##. . .

L5 ANSWER 13 OF 15 USPATFULL
AN 2000:67764 USPATFULL
TI Estrogen agonist/antagonists treatment of atherosclerosis
IN Aiello, Robert J., Waterford, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 6069175 20000530
AI US 1997-955062 19971021 (8)
PRAI US 1996-31275P 19961115 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Richardson, Peter C., Benson, Gregg C., Collier, Steven W.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 566
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of treating atherosclerosis, independent of lipid lowering, in mammals, induding humans, in need of treatment by inhibiting progression of an atherogenic lesion or by stabilizing plaque. Such lesion progression inhibition or plaque stabilization is preferably achieved by directly inhibiting chemokine expression leading to excessive inflammatory cell recruitment by administering certain estrogen agonist/antagonists.
SUMM . . . 500,000 deaths in the United States alone. Coronary artery stenosis and the number of diseased vessels are accepted markers of **cardiac** morbidity and mortality. The rupture of unstable atherosclerotic plaques contributes to nearly 75% of all myocardial infarctions and strokes. However,. . .
SUMM Also, Wiseman, et al. Biochem. Pharm. 45, No. 9, 1851 (1993) have described the role of lipid peroxidation in **cardiovascular** injury and the development of atherosclerosis. In addition, Wiseman et al. Cancer Letters 66, 61 (1992) have disclosed that droloxifene. . .
SUMM The preferred estrogen agonist/antagonists are tamoxifen, 4-hydroxy tamoxifen, raloxifene, **toremifene**, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol and {4-[2-(2-Aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone and pharmaceutically acceptably salts thereof.
DETD Another preferred estrogen agonist/antagonist is **toremifene**: (ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-,2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. patent 4,996,225 (the disclosure of which is hereby incorporated by reference).
DETD Fed a Western-type diet containing 21% fat and 0.15% **cholesterol** (% by weight) (Harlan Teklad, Madison, Wis., Cat. #TD 88137 TEKLAD) for 3 months prior to sacrifice.
DETD . . . to sacrifice. The animals are anesthetized and a whole blood sample is removed from each animal for analysis of plasma **cholesterol** and triglycerides. The mice are perfused in situ with PBS (via heart puncture in the left ventricle) for a short. . .

DETD . . . were fed an adjusted calories "Western-type" diet (Harlan Teklad, Madison, Wis., Cat. # TD 88137, containing 21% fat and 0.15% **cholesterol** by weight). At weaning (age 28 days), female mice were bilaterally ovariectomized (OVX) or sham operated through a one centimeter. . .

DETD . . . up from the base of the heart, the sinus began at the first appearance of the valve cusps dividing the **lumen** into three distinct regions. In this region, the aortic wall is bulging and irregular. The sinus region ends and the valve region begins when the valve cusps no longer divide the **lumen** and the wall appears more rounded and distinct. The valve began at the end of the sinus and continued until. . .

DETD . . . lesion size per section or as the percent of the total cross sectional vessel wall area (normal+diseased area/section, excluding the **lumen**) stained with Oil red O. For each animal, the average of 12 to 16 sections was determined and data are. . .

DETD Total plasma **cholesterol** and triglycerides were measured using calorimetric methods with commercially available kits (Wako and Boehrringer-Mannheim).

DETD . . . data demonstrates the reduction in atherosclerotic lesion size for the estrogen agonist {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone. Importantly, this occurred without a reduction in **cholesterol** as the **cholesterol** lowering activity of the estrogen agonist was not observed in this experiment, either because the compound was administered subcutaneously rather. . .

DETD TABLE

{4-[2-(2-Aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone Reduces Lesion Size in OVX apoE-Deficient Mice Without Affecting Plasma Lipids or Uterine Weight

| Group | N | Total **Cholesterol** (mg/dl) | Triglycerides (mg/dl) | Uterine WT (gm) | Aortic Valve Lesion area (%) |
|---|---|---|---|---|---|
| Placebo | 15 | 929 .+-. 315 | 96 .+-. 24 | | 37 .+-. 39 |

. . .

CLM What is claimed is:

. . . mammal in need thereof, a therapeutically effective amount of a member selected from the group consisting of 4-hydroxy tamoxifen, raloxifene, **toremifene**, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol or {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, or the pharmaceutically acceptable salts thereof, and combinations thereof.

8. A method as recited in claim 2 wherein the compound is **toremifene**.

L5 ANSWER 14 OF 15 USPATFULL

AN 1998:72634 USPATFULL

TI Prevention and treatment of **cardiovascular** pathologies

IN Grainger, David J., Cambridge, England
Metcalfe, James C., Cambridge, England

Kunz, Lawrence L., Redmond, WA, United States
Schroff, Robert W., Edmonds, WA, United States
Weissberg, Peter L., Cambridge, England
PA NeoRx Corporation, Seattle, WA, United States (U.S. corporation)
PI US 5770609 19980623
AI US 1995-486334 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1994-242161, filed on 12 May 1994 which is a continuation-in-part of Ser. No. US 1993-61714, filed on 13 May 1993, now abandoned And a continuation-in-part of Ser. No. US 1994-241844, filed on 12 May 1994 which is a continuation-in-part of Ser. No. US 1993-62451, filed on 13 May 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-11669, filed on 28 Jan 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Henley, III, Raymond
LREP Schwegman, Lundberg, Woessner & Kluth, P.A.
CLMN Number of Claims: 56
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 4318
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1## wherein Z is C.dbd.O or a covalent bond; Y is H or O(C.sub.1 -C.sub.4)alkyl, R.sup.1 and R.sup.2 are individually (C.sub.1 -C.sub.4)alkyl or together with N are a saturated heterocyclic group, R.sup.3 is ethyl or chloroethyl, R.sup.4 is H or together with R.sup.3 is --CH.sub.2 --CH.sub.2 -- or --S--, R.sup.5 is I, O(C.sub.1 -C.sub.4)alkyl or H and R.sup.6 is I, O(C.sub.1 -C.sub.4)alkyl or H with the proviso that when R.sup.4, R.sup.5, and R.sup.6 are H, R.sup.3 is not ethyl; or a pharmaceutically acceptable salt thereof, effective to activate or stimulate production of TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compounds include idoxifene and salts thereof. Further provided is a method for identifying a compound that is a TGF-beta activator or production stimulator is provided. Another embodiment of the invention is an assay or kit to determine TGF-beta in vitro. Also provided is a therapeutic method comprising inhibiting smooth muscle cell proliferation associated with procedural vascular trauma employing the administration of tamoxifen or structural analogs thereof, including compounds of formula (I).
TI Prevention and treatment of **cardiovascular** pathologies
AB A method for treating or preventing **cardiovascular** pathologies by administering a compound of the formula (I): ##STR1## wherein Z is C.dbd.O or a covalent bond; Y is. . .
SUMM This invention relates generally to the prevention and treatment of **cardiovascular** pathologies. More specifically, a method for treating or preventing atherosclerosis is provided.
SUMM . . . in many patients with coronary artery disease. PTCA can relieve myocardial ischemia in patients with coronary artery disease by reducing **lumen** obstruction and improving coronary flow. The use of this surgical procedure has grown rapidly, with 39,000 procedures performed in 1983,. . .
SUMM In general, atherosclerosis is a **cardiovascular** disease in which the vessel wall is remodeled, compromising the **lumen** of the vessel. The atherosclerotic remodeling process involves accumulation of cells, both smooth muscle cells and monocyte/macrophage inflammatory cells, in. . .
SUMM Thus, a need exists for therapeutic methods and agents to treat

**cardiovascular** pathologies, such as atherosclerosis and other conditions related to coronary artery disease.

SUMM A therapeutic method for preventing or treating a **cardiovascular** indication characterized by a decreased **lumen** diameter is provided. The method comprises administering to a mammal at risk of, or afflicted with, said **cardiovascular** indication, a cytostatic dose of a TGF-beta activator or production stimulator. The cytostatic dose is effective to activate or stimulate. . .

SUMM A therapeutic method is provided for treating or preventing **cardiovascular** pathologies, such as conditions selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke. The method comprises the. . .

SUMM A further embodiment of the invention is a method for preventing **cardiovascular** pathologies in a mammal at risk of such a condition. Such conditions include atherosclerosis, thrombosis, myocardial infarction, and stroke. The. . .

SUMM The delivery of TGF-beta activators or production stimulators to the **lumen** of a vessel via catheter, before, during or after angioplasty, is discussed in detail below. A stent or shunt useful. . .

SUMM In addition, methods for using TGF-beta to maintain and increase vessel **lumen** diameter in a diseased or injured mammalian vessel are described.

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats and these studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by the non-TMX analogs of formula (I), including the TMX analog **toremifene** and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD Also included within the scope of the term tamoxifen are the TMX structural analogs **toremifene** and raloxifene, metabolites or pharmaceutically acceptable salts thereof. Other "antisteroids" or "steroidal antagonists" can also be useful as TGF-beta activators. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . suppressing the pathological proliferation of the target cell population. The preferred dosage forms can also release compounds that increase vessel **lumen** area and blood flow, reducing the pathological alterations produced by this reduced blood supply.

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the tunica media smooth muscle cells lining the **lumen** to the dosage form. This dosage is determinable empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD In hypertension, there is increased thickness of the vessel media, with a consequent decrease in maximum **lumen** diameter, leading to increased vascular resistance. The increased thickness of the vessel media is due to growth of VSMC within. . .

DETD . . . proliferate in the intima. There they secrete extracellular matrix proteins and form a lipid-rich plaque that encroaches on the vascular **lumen**. This process is similar to, but slower than, the process that occurs following PTCA, leading to restenosis. Such inappropriate intimal. . .

DETD . . . diet, and also in apoE knockout mice fed a normal diet. Another animal model useful in screening agents is the **cholesterol**-fed Watanabe rabbit. Finally, small scale, pilot studies on candidate molecules are tested in patient groups with clinically significant coronary artery. . .

DETD . . . In addition, heparin coupled to agarose beads (Sigma Chemical Co., St. Louis, Mo.) was examined (see also Grainger et al., **Cardiovascular** Res. 27:2238-47, 1993).

DETD . . . whether the mice were fed a normal diet (Techlad, Madison, Wisconsin; 4% mouse/rat chow) or a lipid-rich diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium chelate.

DETD . . . by increasing TGF-.beta. activity, such as TMX (Grainger et al., Biochem. J., 294, 109 (1993)) and heparin (Grainger et al., **Cardiovas**. Res., 27 2238 (1993)), inhibited the proliferation of EX but not ED cells.

DETD . . . in groups were weighed then fed ad libitum either normal mouse chow (ICN/Flow), or a high fat diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium cholate, or high fat diet containing 15 .mu.g TMX. . .

DETD . . . The column was eluted with buffer A at 0.4 ml/minute and fractions of 0.2 ml were collected and analyzed for **cholesterol**. **Cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) by adding 5 .mu.l from each column fraction to 200 .mu.l assay reagent in an ELISA. . . incubated at 37.degree. C. for 15 minutes and absorbance read at 492 nm. Serum for calibration containing 200 mg/dL total **cholesterol** (Sigma Diagnostics) was used to convert absorbance readings to **cholesterol** concentrations according to the manufacturer's instructions. The positions of elution of the major lipoprotein classes in mouse platelet-poor plasma under. . .

DETD Assays for Plasma Triglycerides, **Cholesterol** and Sex Hormones Total plasma triglycerides was measured by the UV end-point glycerol kinase enzymatic method (Sigma Diagnostics). Total plasma **cholesterol** was measured by the **cholesterol** oxidase method (Sigma Diagnostics) performed in ELISA plate wells as described above. 17-.beta.-estradiol was measured by a specific sandwich ELISA. .

DETD . . . on either a normal mouse chow (low fat diet), or a high fat chow containing 0.5% sodium cholate and 5% **cholesterol** (high fat diet), or high fat diet containing 15 .mu.g/g TMX (high TMX diet). The mice on the high TMX. . .

DETD . . . .+-.

3 13 .+-.

5 11 .+-.

7

Testosterone (ng/ml) Total Plasma

71 .+-.

2 92 .+-.

4* 79 .+-.

3** 83 .+-.

4***

**Cholesterol** (mg/dl) VLDL 4 30 38 42

**Cholesterol** (mg/dl) LDL 8 33 27 27

**cholesterol**
(mg/dl)
HDL- 58 27 11 14
**cholesterol**
(mg/dl)
Total 142 .+-.
15 109 .+-.
5* 111 .+-.
9 204 .+-.
36***
Triglycerides
(mg/dl)
SM-.alpha.-actin
146 .+-.
6 138 .+-.
8 168 .+-.

. . .

DETD High or low TMX diets significantly lowered total plasma **cholesterol** by approximately 10% compared with mice on the high fat diet. Analysis of the lipoprotein profiles showed that for the mice on the low fat diet, most of the **cholesterol** was in the HDL fraction. After 3 months on the high fat diet, however, there was a marked increase in very low density lipoprotein (VLDL) **cholesterol** of approximately 7-fold (Table 2) and LDL **cholesterol** (4-fold) whereas the amount of **cholesterol** in the HDL fraction was reduced by approximately 50% (Table 2). The high and low TMX diets had only small effects on the amount of **cholesterol** in VLDL or LDL, but further reduced the HDL **cholesterol** by approximately 50% (Table 2), accounting for most of the overall reduction in **cholesterol**. In contrast to the decrease in total plasma **cholesterol** concentration caused by the high TMX diet, there was an increase in plasma concentration of triglyceride (Table 2).

DETD . . . subsequently uptake of lipid by the activated cells when the mice are subjected to a high fat diet. Thus, the **cardiovascular** protective effect of TMX in mice may be due to elevation of TGF-.beta. in the artery wall which prevents VSMC. . . . TMX would prevent lipid lesion formation in apo(a) mice on a high fat diet. It is of interest that the **cardiovascular** protective effects of TMX against diet-induced lipid lesions in mice reported here were obtained at doses similar to those used. . .

CLM What is claimed is:

4. The method of claim 1 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a pharmaceutically acceptable salt thereof.

14. The method of claim 14 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, **toremifene**, or a pharmaceutically acceptable salt thereof.

33. The method of claim 24 wherein the compound is **toremifene**, or a pharmaceutically acceptable salt thereof.

35. The method of claim 1 or 13 wherein the compound is **toremifene**, or a pharmaceutically acceptable salt thereof.

52. The method of claim 51 wherein the compound is droloxifene, raloxifene, **toremifene**, tamoxifen, idoxifene, or a pharmaceutically acceptable salt thereof.

L5 ANSWER 15 OF 15 USPATFULL
AN 97:5708 USPATFULL
TI Method for identifying an agent which increases TGF-beta levels
IN Grainger, David J., Cambridge, England
Metcalfe, James C., Cambridge, England
PA NeoRx Corporation, Seattle, WA, United States (U.S. corporation)
PI US 5595722 19970121
AI US 1995-476735 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1994-242161, filed on 12 May 1994 which is a continuation-in-part of Ser. No. US 1993-61714, filed on 13 May 1993, now abandoned And Ser. No. US 1994-241844, filed on 12 May 1994 which is a continuation-in-part of Ser. No. US 1993-62451, filed on 13 May 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-11669, filed on 28 Jan 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Henley, III, Raymond
LREP Schwegman, Lundberg, Woessner & Kluth, P.A.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 4090
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for identifying a compound that is a TGF-beta activator or production stimulator is provided.
SUMM This invention relates generally to the prevention and treatment of **cardiovascular** pathologies. More specifically, a method for treating or preventing atherosclerosis is provided.
SUMM . . . in many patients with coronary artery disease. PTCA can relieve myocardial ischemia in patients with coronary artery disease by reducing **lumen** obstruction and improving coronary flow. The use of this surgical procedure has grown rapidly, with 39,000 procedures performed in 1983,. . .
SUMM In general, atherosclerosis is a **cardiovascular** disease in which the vessel wall is remodeled, compromising the **lumen** of the vessel. The atherosclerotic remodeling process involves accumulation of cells, both smooth muscle cells and monocyte/macrophage inflammatory cells, in. . .
SUMM Thus, a need exists for therapeutic methods and agents to treat **cardiovascular** pathologies, such as atherosclerosis and other conditions related to coronary artery disease.
SUMM A therapeutic method for preventing or treating a **cardiovascular** indication characterized by a decreased **lumen** diameter is provided. The method comprises administering to a mammal at risk of, or afflicted with, said **cardiovascular** indication, a cytostatic dose of a TGF-beta activator or production stimulator. The cytostatic dose is effective to activate or stimulate. . .
SUMM A therapeutic method is provided for treating or preventing **cardiovascular** pathologies, such as conditions selected from the group consisting of atherosclerosis, thrombosis, myocardial infarction, and stroke. The method comprises the. . .
SUMM A further embodiment of the invention is a method for preventing **cardiovascular** pathologies in a mammal at risk of such a condition. Such conditions include atherosclerosis, thrombosis, myocardial infarction, and stroke. The. . .
SUMM The delivery of TGF-beta activators or production stimulators to the **lumen** of a vessel via catheter, before, during or after angioplasty, is discussed in detail below. A stent or shunt useful. .
.

SUMM In addition, methods for using TGF-beta to maintain and increase vessel **lumen** diameter in a diseased or injured mammalian vessel are described.

DETD . . . TMX has been attributed to the formation of covalent DNA adducts. Of the TMX analogs and derivatives, only TMX and **toremifene** have been studied for long-term carcinogenicity in rats and these studies provide strong evidence that covalent DNA adducts are involved in rodent hepatocarcinogenicity of TMX. **Toremifene**, which exhibits only a very low level of hepatic DNA adducts, was found to be non-carcinogenic. See Potter et al.,. . .

DETD . . . hypothesis explains the low level of DNA adduct formation by the non-TMX analogs of formula (I), including the TMX analog **toremifene** and the absence of DNA adducts detected for the analogs 4-iodotamoxifen and idoxifene. Thus, all of these analogs are likely. . .

DETD Also included within the scope of the term tamoxifen are the TMX structural analogs **toremifene** and raloxifene, metabolites or pharmaceutically acceptable salts thereof. Other "antisteroids" or "steroidal antagonists" can also be useful as TGF-beta activators. . .

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the intimal or tunica media cells lining the **lumen** thereto. Also, such a dosage can be determined empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD . . . suppressing the pathological proliferation of the target cell population. The preferred dosage forms can also release compounds that increase vessel **lumen** area and blood flow, reducing the pathological alterations produced by this reduced blood supply.

DETD . . . dosage sufficient to expose the proximal (6 to 9) cell layers of the tunica media smooth muscle cells lining the **lumen** to the dosage form. This dosage is determinable empirically, e.g., by a) infusing vessels from suitable animal model systems and. . .

DETD In hypertension, there is increased thickness of the vessel media, with a consequent decrease in maximum **lumen** diameter, leading to increased vascular resistance. The increased thickness of the vessel media is due to growth of VSMC within. . .

DETD . . . proliferate in the intima. There they secrete extracellular matrix proteins and form a lipid-rich plaque that encroaches on the vascular **lumen**. This process is similar to, but slower than, the process that occurs following PTCA, leading to restenosis. Such inappropriate intimal. . .

DETD . . . diet, and also in apoE knockout mice fed a normal diet. Another animal model useful in screening agents is the **cholesterol**-fed Watanabe rabbit. Finally, small scale, pilot studies on candidate molecules are tested in patient groups with clinically significant coronary artery. . .

DETD . . . In addition, heparin coupled to agarose beads (Sigma Chemical Co., St. Louis, Mo.) was examined (see also Grainger et al., **Cardiovascular** Res. 27:2238-47, 1993).

DETD . . . whether the mice were fed a normal diet (Techlad, Madison, Wis.; 4% mouse/rat chow) or a lipid-rich diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium chelate.

DETD . . . by increasing TGF-.beta. activity, such as TMX (Grainger et al., Biochem. J., 294, 109 (1993)) and heparin (Grainger et al., **Cardiovas**. Res., 27, 2238 (1993)), inhibited the proliferation of EX but not ED cells.

DETD . . . in groups were weighed then fed ad libitum either normal mouse chow (ICN/Flow), or a high fat diet containing 1.25% **cholesterol**, 7.5% saturated fat as cocoa butter, 7.5% casein and 0.5% sodium cholate, or high fat diet containing 15 .mu.g TMX. . .

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DETD . . . .+-. 3

13 .+-. 5

11 .+-. 7

Testosterone
(ng/ml)
Total Plasma

71 .+-. 2

92 .+-. 4*

79 .+-. 3**

83 .+-. 4***

**Cholesterol**
(mg/dl)
VLDL 4 30 38 42

**Cholesterol**
(mg/dl)
LDL 8 33 27 27

**cholesterol**
(mg/dl)
HDL- 58 27 11 14

**cholesterol**
(mg/dl)
Total 142 .+-. 15

109 .+-. 5*

111 .+-. 9

204 .+-. 36***

Triglycerides
(mg/dl)
SM-.alpha.-actin

146 .+-. 6

138 .+-. 8

168 .+-.. . .

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